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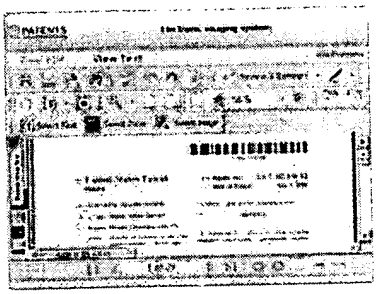

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Applicant	CAPELLI CHRISTOPHER C (US)
Inventor	CAPELLI CHRISTOPHER C (US)
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Claims

CLAIMS

I claim:

An antimicrobial composition. comprising silver thiosulfate ion complexes in a base.

2. The composition of Claim 1. wherein said silver thiosulfate ion complexes are homogeneously suspended in said base.

The composition of Claim I, wherein said base isanhydrous 4 The composition of Claim I. w'herein the concentrationof said silverthiosulfate ion complexes within said base is from 0.01% to 30% (w/w)

The composition of Claiml, wherein the concentration of said silver thiosulfate ion complexes within said base Is from 0.1% to3.0% (w/w) 6. The composition of Claim 1. wherein the concentration of said silver thiosulfate ion complexes within said base is from 0.2% to1.5% (w/w) 7 The composition of Claim I. wherein said base Is selected from the group consisting ofpolyethylene glycol.Aquaphor#. and whitepetroiatum The composition of Claim I,wherein said silver thiosulfate ion complexes are derived from the complexation of a silver cation from silverhalides with anions.

The composition of Claim 8. wherein said silver halide comprises silver chloride and said anions comprise sodium thiosulfate salts.

10. The composition of Claim 9. wherein the molar ratio of the thiosulfate anions to silver cations is at least I I

II The composition of Claim 9. wherein the molar ratio of thiosulfate anions to silver cations is at least 1.3.1.

12. A pharmaceutical mixture. comprising:

a) a medicinal agent: and

b) silver thiosulfate ion complexes.

13. The pharmaceutical mixture of Claim 12, wherein said silver thiosulfate ion complexes are carrier-free.

14. The pharmaceutical mixture of Claim 12. further comprising an anhydrous base.

15 The pharmaceutical mixture of Claim13, wherein said base Is selected from the group consisting ofpolyethvlene glycol. Aquaphor . and white petrolatum.

16. The pharmaceutical mixtureot Claim1 2 whereinthe concentration of said silver thiosulfate ion complexes in said pharmaceutical mixture is from 0 01% to30% (w/w) 17 The pharmaceutical mixture of Claim I 2. wherein the concentration of said silver thiosulfate ion complexes in said pharmaceuticalmixture Isfrom 0.1% to 3 0%(wXw) 18 The pharmaceutical mixture of Claim12, wherein the concentration of said silverthlosulfate ion complexes in said mixture isfrom 0.2% to I5% (w/w) 19. The pharmaceutical mixture of Claim 12, wherein said medicinal agent of said pharmaceutical mixture is an antimicrobial agent.

20. The pharmaceutical mixture of Claim 19, wherein said antimicrobial agent is selected from the group consisting ofacvclovir, chloramphenicol, chlorhexidine.

chlortetracycline, itraconazole. mafenide. metronidazole. mupirocin. nitrofurazone, oxvtetracycline, penicillin, and tetracycline.

2 1. The pharmaceutical mixture of Claim 12, wherein said medicinal agent of said pharmaceutical mixture is a steroid.

22. The pharmaceutical mixture of Claim 21, wherein said steroid is selected from the group consisting of betamethasone benzoate, betamethasone valerate, desonide, fluocinolone acetonide, halcinonide, hydrocortisone, and metandienone.

23 The pharmaceutical mixture of Claiml 2. wherein said medicinal agent of said pharmaceutical mixture is an anesthetic.

94. The pharmaceutical mixture of Claim23, wherein said anesthetic is selected from the group consisting ofbenzocaine. dibucaine. lidocaine, pramoxine hvdrochloride and tetracacine.

25. A method of imparting antimicrobial protection. comprising.

a) providing:

l) a product. and

ii) an effective amount of carrier-free suspended silver thiosulfate ion

complexes: and

b) applying the effective amount of the carrier-free suspended silver thiosulfate

ion complexes in a base to the object.

26. The method of Claim 25. wherein said product is solid.

27. The method of Claim 26. wherein said product Is a medical device.

28. The method of Claim 27.wherein said medical device comprises a matrix.

29. The method of Claim 28, wherein said matrix Is a polymer.

30. The method of Claim 29. wherein said polymer is anhvdrous.

3 1 The method of Claim 25. wherein product is a personal care product.

32. The method of Claim3 1. wherein said personal care product is selected from the group consisting ofdipsticks. lipgloss, lip pencils, mascaras. eye liners. eye shadows, moisturizers, liquid makeup foundations, powder makeup foundations. powder blushes, cream blushes. perfumes. colognes,tones. deodorants, shaving creams, shampoos, conditioners, hair mousses. hairsprays, toothpastes. and mouthwashes.

33 The method of Claim 2S.wherein said personal care product Is selected from the group consisting of combs. brushes, sponges, cotton swabs, cotton balls, razors, dentaltosses dental tapes, sunscreens, moisturizers, tampons. sanitary napkins. panty shields, diapers, baby wipes, facial tissues and toilet tissues.

34.A device, comprising a medical device coated with an antimicrobial compositions comprising silverthiosulfate ion complexes.

35 The device of Claim i4wherein said medical device Is selected from the group consisting of medical implant.wound care devices. body cavitv and personalprotection devices.

36 The device of Claim34. wherein said device is aurinarv catheter and said silver thiosulfate ion complexes comprise an anhydrous polymer matrix37 A method of treating or preventing a microbial infection. comprising:

a) providing:

i) a subject. said subject either infected or at risk of infectionbv a topical

microbial infection, and

ii) aneffective amount of carrier-free suspended silver thiosulfate ion

complexes in a base to form a pharmaceutical mixture; and

b) administering the effective amount of the carrier-free suspended silver

thiosulfate ion complexes in a base to the subject.

38 The method of Claim 37. wherein said silver thiosulfate ion complexes are carrier-free.

39 The method of Claim 37. wherein said base is anhydrous.

40. The method of Claim 39. wherein said base is selected from the group consisting of polyethylene glycol.AquaphorUR. and white petrolatum.

41 The method of Claim 37 wherein the concentration of said silver thiosulfate ion complexes in said pharmaceutical mixture is from 0 01% to 30% (w/w) 42. The method of Claim 37. wherein the concentration of said silver thiosulfate ion complexes in said pharmaceutical mixture is from 0 1% to3 0% (w/w).

43. The method of Claim37. wherein the concentration of said silver thiosulfate ion complexes In said mixture is from 0.2% to 1.5% (w/w) 44. The method of Claim 37, wherein said pharmaceutical mixtureforther comprises a medicinal agentAS The method of Claim 44.wherein saidmedicinal agent is a microbial agent.

46. The method of Claim 45. wherein said antimicrobial agent Is selected from the group consisting of acyclovir, chloramphenicol, chlorhexidine, chlortetracycline,@traconazole, mafenide, metronidazole, mupirocin, nitrofurazone, oxytetracycline, penicillin, and tetracycline.

47. The method of Claim 44. wherein said medicinal agent of said pharmaceutical mixture is a steroid.

48. The method of Claim 47. wherein said steroid is selected from the group consisting of betamethasone benzoate. betamethasone valerate. desonide. fluocinolone acetonide, halcinonide, hydrocortisone. and metandienone.

49. The method of Claim 44. wherein said medicinal agent of said pharmaceutical mixture is an anesthetic.

50 The method of Claim 49, wherein said anesthetic is selected from the group consisting of benzocaine, dibucaine. lidocaine, pramoxine, hydrochlonde and tetracacine.

51 A method for producing essentiallyanhydrous silver thiosulfate ion complexes, comprising:

a)iiroviding an aqueous solution of silver thiosulfate ion complexes.

b) adding a solvent to said solution to create a biphasic separation wherein said

silver thiosulfate ion complexes separate into a single phase,

c) collecting said single phase containing said silver thiosulfate ion complexes:

and

d) removing water from said single phase such that said silver thiosulfate ion

complexes are essentially anhydrous.

52 The method of Claim 51wherein the ratio of thiosulfate ions to silver ions in said silver thiosulfate ion complexes is greater at least2. Is3 The method of Claim52 wherein the ratio ofthiosulf'ate ions to silver ions in said silver thiosulfate ion complexes is less than 3.1 54 The method of Claim 51. wherein said aqueous solution is formedbv reacting a silver halide with sodium thiosulfate.

55. The method of Claim 54. wherein the molar ratio of silver cations from said silver halide to thiosulfate anions from said sodium thiosulfate Is at least I 56. The method of Claim 55, wherein the molar ratio of silver cations from said silver halide to thiosulfate anions from said sodium thiosulfate Is at least 1.3.1.

57. The method of Claim 54. wherein said silver halide comprises silver chloride.

58 The method of Claim51. wherein said solvent is water-miscible.

59 The method of Claim58. wherein said solvent is selected from the group consisting of ethyl alcohol. isopropyl alcohol, methyl alcohol, acetone. andtetrahvdrofuran.

GOA method for producing essentiallyanhvdrous silver thiosulfate ion complexes, comprising

a) providing an aqueous solution of silver thiosulfate ion complexes:

b) adding a solvent to said aqueous solution to precipitate said silver thiosulfate

ion complexes

c) collecting said precipitated silver thiosulfate ion complexes: and

d) removing water from said collected silver thiosulfate ion complexes such that

said silver thiosulfate ion complexes are essentially anhydrous.

6 1. The method of Claim 60,wherein the ratio of thiosulfate ions to silver ions in said silver thiosulfate ion complexes Is less than'.

62 The method of Claim 61. wherein the ratio of thiosulfate ions to silver ions in saidsilver thiosulfate ion complexes Is greater than I I 63. The method of ClaimoO. wherein said aqueous solution of silverthiosulfate ion complexes isformed by reacting silver halide with sodium thiosulfate.

64. The method of Claim 63. wherein the molar ratio of silver cationsfrom said silver halide to thiosulfate anions from said sodium thiosulfateisat least I I 65. The method of Claim 63, wherein the molar ratio of silver cations from said silver halide to thiosulfate anions from said sodiumthiosuifate is at least 1.3:1.

66. The method of Claim 63. wherein said silver halide is silver chloride.

67 The method of Claim60, wherein said solvent is water-miscible.

68. The method of Claim 67. wherein said solvent is selected from the group consisting of ethyl alcohol, isopropyl alcohol. methyl alcohol, acetone, and tetrahydrofuran.

Description

SILVER-BASED ANTIMICROBIAL COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to silver-based antimicrobial compositions and processes for making such compositions that are suitable for use in the treatment and prevention of infectionsBACKGROUND OF THE INVENTION1. Antimicrobial Agents

Antimicrobial agents are chemical compounds that either destrov microbes prevent theirpathogenic action. or prevent their growth Antimicrobial agents. often referred to asanti-infective agents. are frequently appliedtopical lav to the skin and mucous membranes in the form of a solution. cream. or ointment: appropriate formulations mav be applied to wounds and body cavities. and to the eves, nose. and mouth.

In general. topical antimicrobial agents are directed at bacteria. viruses. and fungi.

They have been usedsuccessfully in the prevention and treatment of a number of infections.

including impetigo. candidiasis. tinea pedis (athlete'sfoot). acne vulgaris. and infections resulting from burns andsuruical wounds.

Most agents have a limited spectrum ofactivitv For example. some are specific for particular gram (+) organisms. while others are specific for particular gram (-) organismsMoreover. bactericidal agentstvpicallv are notfungicidal. whilefuntzicidal agents tvpicallv are not bactericidal

In addition. due to the widespread use and frequentover-prescribing of antimicrobial agents. there is an increasing incidence of microbes acquiringdruy-resistance In other words.

a microbe that was once susceptible(i.'?. inhibited or killed) to a particular antimicrobial agent is no longer susceptible. This is especially important with regard to bacteria.

Acquired drug resistance is usually causedbv a mutation within thegnome of the microbe or by the acquisition ot' a plasmid For example. one of the major mechanisms of resistance to thess-lactam antibiotics. including penicillins. Is the production of of ss-lactamases

Moreover. resistance to one member of a class of agents (e.g., theaminopenicillin ampicillin) can result in complete cross-resistance to other members of that class (e.g., the aminopenicillin amoxicillin) II. Topical Silver-Containing Agents

A. Currently Used Therapeutic Agents

Two formulations containing silver have been utilized for therapeutic purposes, silver nitrate and silver

sulfadiazine. As set forth hereafter, each is associated with potentially severe adverse effects and other limitations.

A1% silver nitrate ophthalmic solution can be used in newborns tor the prophylaxis of gonococcal ophthalmia (gonococcal ophthalmia neonatorum). Because the silver ion is precipitated by chloride, the silver nitrate solution does not readily penetrate into tissue.

Unfortunately, the silver salts stain tissue black as a result of the deposition of reduced silver; some of the staining mav persist indefinitely. Thus, silver nitrate is not used topically for other indications (e.g., Impetigo).

Silver sulfadiazine1% topical cream Isroutinelv used as an adiunct in the prevention and treatment of infection in burn victims. [See U S. Patent No. 3,761,590 to Fox. hereby incorporatedbv reference] Silver sulfadiazine. produced by the reaction of silver nitrate with sulfadiazine. has been associated with necrosis of the skin. In addition. sulfadiazine mav accumulate in patients with impaired hepatic or renal function. requiring in severe cases examination of thepatients urine for sulfonamide crystals. Moreover. patients allergic to sulfa agents may exhibit cross-hypersensitivity with silver sulfadiazine. [See generally; AHFS

Drug Information. Gerald K. McKevoy, ed., pp. 1704-05 and 2215-16 (1993)]

B. Newer Antimicrobial Silver-ContainingCompositions

One of the reasons whvthere arefew commerciallv availablesilver-containin therapeutic formulations is the difficulty of making such formulations photostable Thatis.

such formulations turn a dark color andfrequently lose antimicrobialefficacy upon short-term (e.g., 3-4 days) exposure to ambient light.

There have been several recent efforts to produce asilver-containino formulation that exhibits high antimicrobial efficacy and photostabilitv. For example, U.S. Patent No 5,326,567 to Capelli. hereby incorporatedbv reference, describes an antimicrobial composition comprising a stabilizing acyclicpolvether polymer, silver ion. and a stabilizing halide The composition may be used in several manners. including topical application to a subject and incorporation into a medical device.

In addition. a new class of silver-containing agents. the silver thiosulfate ion complexes. has recentiv been disclosed in U.S Patent No 5,429,819 to Oka etcurl. (hereafter "the Oka Patent").herebv incorporatedbv reference.{NL'L' also Tomiokact al.,"Svnthesis of

Antimicrobial Agent Composed ofSiiver-Thiosulfate Complexlon." Nippon Kagaku Kaishi 10:848-50 (1995)]. The Oka Patent describes an antiviral composition that contains i) a thiosulfate salt and ii) at least one thiosulfate complex salt of a metal and iii) a porous particulate carrier; the metal is either silver, copper or zinc. and the salts are carried on the porous particulate carrier. According to the Oka Patent's teachings, the thiosulfate complex salt and thiosulfate metal complex salt are first prepared as a solution. Thereafter. a porous carrier such as silica gel is impregnated with the solution Finally. the thiosulfate complex and thiosulfate metal complex salt are immobilized on the porous carrier through drving.

This metal-containing porous carrier is then formulated into the compositions described in the

Oka Patent.

The antimicrobial compositions taught in the Oka Patent are associated with several notable shortcomings. First. the silver thiosuifate ion complex compositions contain arelativelv large concentration of waste salts. resulting from the complexation of a thiosulfate salt. sulfite salt. and a silver salt, and are thusrelativelv impure. Forexample, producing I part of a silver thiosulfate ion complex using I part of silver nitrate (or silver acetate) to2 parts sodium thiosulfate and/or2 parts sodium sulfite will result in I part waste sodium nitrate(or sodium acetate); the inclusion of these salts results in a lower concentration of silver.

Similarly, as indicated above. the silver thiosulfate ion complex requires the use of porous carrier particles; the necessity of these carrier particlesiimits the concentration of thiosulfate complex salt and thiosulfate metal complex salt. Thus, the amount of porous carrier particles needed to provide silver at antimicrobial concentrations ishigh. and. as a result. a topical antimicrobial composition would feel grittv and would beirritating to the skin or wound. In addition. if the concentration of thiosulfate complex salt and thiosulfate metal complex salt carried on the porous carrier is too high, the composition may discolor.

Finally, the compositions taught by the Oka Patent cannot be easily incorporated into a polymer matrix at high concentrations. As stated above. incorporation of silver at antimicrobial concentrations requires concomitant incorporation of a large amount of porous carrier. This can cause undesirable changes in the polymer matrix'phvsical properties(c.S. a hvdrocolloidmatnx that is stiff and less absorptive). In addition.

such incorporation can beunwieldv. For example, in an alginate matrix containingwater-insoluble fibers, the silvercontaining porous carrier cannot be incorporated into thealginate fibers: as a result. the porous carrier must be mixed loosely within the alginate fibers. Unfortunately, the porous carrier can fall out when the alienate matrix is handled.

From the above. it should be clear that thecommerciallv-available silver-based antimicrobial agents have limited applications and can be associated with severe adverseeffects Moreover many recent efforts to develop a topicalsilver-containiny formulation are connected with drawbacks. asexempiified bv the prior art requirement of a carrier What Is needed is a stable silver-containing antimicrobial composition which is suitable for use in the treatment and prevention of a broad range of infections and that is not associated with the adverse effects andiimitations of the agents that have previously been described

SUMMARY OF THE INVENTION

The present invention relates generally to silver-based antimicrobial compositions and processes for making such compositions suitablefor use in the treatment and prevention ofinfections In particular. the present invention relates to stable silver-based antimicrobial compositions and processes tor making such compositions.comprising carrier-free. suspended silver thiosulfate ion complexes in a base Preferably, the silver thiosulfate ion complexes arehomogeneously suspended in ananhvdrous base.Alternatively, the silver thiosulfate ion complexes of the present invention can be incorporated into a matrix and used with a medical device Pharmaceutical compositions can also be producedbv combining the silver thiosulfate ion complexes with medicinal agents. including but not limited to antimicrobial agents.

steroids. and anesthetics.

One advantage of providing silver thiosulfate ion complexes in a carrier-free form Is theabilitv to produce antimicrobial compositions containing high concentrations of silver thiosulfate ion complexes so as to provide potentantimicrob@al activitv \ further advantageot' the carrier-free compositions is the elimination of irritation that mav result from the carrier upon topical administration. Thus. the invention contemplates a method of treating or preventing infections in comprising applying topically to the site (or potential site)ot infection an effective amount of theforegoing composition

As alluded to above. the invention also contemplates methods ot' making the stable silver-based antimicrobial compositions It is preferred that the silver complexes of the present invention are derived from the complexation of silver cations from silverl1alides (preferably silver chloride) with anions from the sodiumthiosulfate salts, the molar ratioof the thiosulfate anions to the silver cations Ispreferablv at least I I and more preferably at least I 3 1 It is desirable that the silver thiosulfate ion complexes are solid and essentially pure. i.e.,thev do not contain significant amounts of waste salts or other substances that interfere with their antimicrobial activity, in addition they do not require carrier particles.

The compositions are able to contain high concentrations of silver thiosulfate ion complexes. thereby providing strong antimicrobial activity.Moreover the compositions maybe used in combination with other pharmaceutical (e.g., topical) agents (e.g., , Bactroban@ [mupirocin], SmithKline Beecham). Such combination mav serve to avoid antimicrobial resistance, increase the spectrum of activity, and have asynergistic effect.

The silver thiosulfate ion complexes of the present invention may be incorporated into medical devices. including medical implants, wound care devices, body cavity and personal protection devices. and the like. By way of illustration. purified silver thiosulfate ion complexes may be incorporated with an anhydrous polymer matrix that is used to coat a urinary catheter in order to prevent infection. Similarly. the silver thiosulfate ion complexes may be used in cosmetics and personal care products to make them resistant to antimicrobial contamination. Examples of cosmetics include lipsticks and glosses. lip pencils, mascaras. eve liners. eve shadows, moisturizers. liquid and powder makeup foundations, powder and cream blushes perfumes.cologne. various creams and toners, etc.. and assorted applicators like combs. brushes. sponges. and cotton swabs and balls. and examples of personal care products include deodorants. razors. shaving creams. shampoos. conditioners. various hair treatments like mousses andspravs, toothpastes, mouthwashes. dental flosses and tapes. sunscreens.

moisturizers. tampons. sanitary napkins.pantv shields, diapers.babv wipes. facial tissues.

toilet tissues. etc.

the present invention contemplates a composition.comprising carrier-free suspended silver thiosulfate ion complexes suspended in a base. In one embodiment. the base isanhvdrous. It is contemplated that the concentration of silver thiosulfate ion complexes within the base issutficient to provide a therapeutic benefit.Specifically. the present invention contemplates concentrations of silver thiosulfate ion complexes within the base from 0 01% to 30% (w/w) and from 0.1% to 3 0% (w/w). The preferred concentration of silver

thiosulfate ion complexes within the base is from 0.2% to1.5% (w/w) In one embodiment, the base Is selected from the group consisting ofpolyethvlene glycol.Aquaphor and white petrolatum.

The present invention also contemplates a method of treating or preventing a topical microbial infection. comprising the steps of a) providing I) a subject infected with a topical microbial infection and ii) an effective amount of carrier-free suspended silver thiosulfate ion complexes in a base: and b) administering topically the effective amount of the carrier-free suspended silver thiosulfate ion complexes In a base to thesubject. thereby treating or preventing the topical microbial infection. In one embodiment. the base is anhydrous.

It is contemplated that the concentration of silver thiosulfate ion complexes within the base Is sufficient to provide a therapeutic benefit. For example the present invention specifically contemplates concentrations of silver thiosulfate ion complexes within the base from 0.01% to30% (w/w) and from0.1% to 30% (w/w) The preferred concentration of silver thiosulfate ion complexes within the base is from 02% to 1 5% (w/w) In one embodiment. the base is selected fromthe group consisting of polyethylene glycol.

Aquaphor@, and white petrolatum.

The present invention further contemplates a method of imparting antimicrobial protection to an object.comprisinet the steps of: a) providing I) an object and ii) an effective amount of carrier-free suspended silver thiosulfate ion complexes. and b) applying the effective amount of thecarrier-free suspended silverthiosulfate ion complexes In a base to the oblect. thereby Imparting antimicrobial protection to the obiect. It is preferred that the object

Is solid and chemically inert.

In one embodiment. the concentration of silver thiosulfate ion complexes is sufficientto provide a therapeutic henetit S pecifically. the present invention contemplates concentrations of silver thiosulfate ion complexes from 0.01% to30% (w/w) and from 01% to 3 0% (w/w) The preferred concentration of silver thiosulfate ion complexes is from 0 2% to Is0Xo (w/w).

In still further embodiments. the oblect Is a medical device In particular embodiments. the medical device comprises amatrix In someembodiments lie matrix Is apolymer. while it Isanhvdrous in still furtherembodiments

The present invention also contemplates a processfor producing essentially anhydrous silverthiosullate ion complexes.comprising a) making an aqueous solution of silver thiosulfate ion complexes: b) adding a solvent to the solution to create a biphasic separation wherein the silver thiosulfate ion complexes separate into one phase.c) collecting the phase containing the silver thiosulfate ion complexes: and d)removing water from the collected phase such that the silver thiosulfate ion complexes are essentiallyanhvdrous In particular embodiments. the ratio of thiosulfate ions to silver ions is greater than or equal to 2. 1 and preferably less than 3 1

In some embodiments. the aqueous solution of silver thiosulfate ion complexes Is formedbv reacting a silver halide and sodium thiosulfate In other embodiments. the molar ratio of silver cations from the silver halide to thiosulfate anions from the sodiumthiosulfate is preferablv at least 1 1 and more preferably at least1.3.1. In still further embodiments. the silver halide is silver chloride.

In other embodiments. the solvent Is water-miscible. The solvent Is selected from the group consisting of ethyl alcohol. isopropyl alcohol,methvl alcohol. acetone, and tetrahydrofuran in certain embodiments.

Additionally. the present invention contemplates a process for producing essentiallyanhvdrous silver thiosulfate ion complexes. comprising: a) making an aqueous solution of silver thiosulfate ion complexes; b) adding a solvent to the solution to precipitate the silver thiosulfate ion complexes; c) collecting the precipitated silver thiosulfate ion complexes: and d) removing water from the collected silver thiosulfate ion complexes such that the silver thiosulfate ion complexes are essentially anhydrous. In particular embodiments. the ratioot thlosultate @ons to silver ions is less than2 1 andpreferably greater than I I

In some embodiments. the aqueous solution of silver thiosulfate ion complexes is formed by reacting a silver halide and sodium thiosulfate. In other embodiments, the molar ratio of silver cations from the silver halide to thiosulfate anions from the sodium thiosulfate is preferably at least I I and more preferably at least 1 3 I In still further embodiments. the silver halide is silver chloride.

In other embodiments, the solvent is water-miscible. The solvent is selected from the group consisting of ethvl alcohol. isopropyl alcohol.methvl alcohol. acetone. andtetrahvdrofuran In certain embodiments

The present invention also contemplates a pharmaceutical mixture. comprising. a) a medicinalagent: and b) silver thiosulfate ion complexes. In preferred embodiments. the silver thiosulfate ion complexes are carrier-

free. In particular embodiments. the pharmaceutical mixture further comprises an anhydrous base; in some embodiments, the base is selected from the group consisting ofpolyethylene glycol. Aquaphor and whitepetrolatum.

In some embodiments of the present invention. the concentration of the silver thiosulfate ion complexes in the pharmaceutical mixture isfrom ().()1% to,() N, (weight to weight). In further embodiments. the concentration of silver thiosulfate ion complexes Is from0.1% to3.0% (weight to weight),while in still further embodiments the concentration is from0.39/0 to 1.5% (weight toweight).

In particular embodiments. the medicinal agent of the pharmaceutical mixture is an antimicrobial agent. In some embodiments. the antimicrobial agent Is selected from the group consisting of acyclovir. chloramphenicol. chlorhexidine chlortetracvcline.itraconazole, mafenide, metronidazole. mupirocin, nitrofurazone. oxytetracycline, penicillin. and tetracycline. When the medicinal agent is an antimicrobial agent. in some embodiments the pharmaceutical mixture has a broader spectrum of antimicrobial protection than the silver thiosulfate ion complexes.

Furthermore. the medicinal agent of the pharmaceutical mixture is a steroid in certain embodiments. In particular embodiments. the steroid is selected from the group consisting of betamethasone benzoate. betamethasone valerate. desonide. fluocinolone acetonide.

halcinonide. hydrocortisone. and metandienone.

Finally, the medicinal agent of the pharmaceutical mixture is an anesthetic in still other embodiments. In certain embodiments. the anesthetic Is selected from the group consisting ofbenzocaine. dibucaine.lidocaine. pramoxine hydrochloride and tetracacine

DEFINITIONS

To facilitate understanding of the invention set fonh in the disclosure that follows. a number of terms are defined below.

The term "carrier" refers to a substance. like an inorganic oxide. in which a material can be impregnated and then.It' necessarv, immobilized throughdrying. For example, the

Oka Patent describes the impregnation of a porous particulate carrier (e.g., silica gel) with a solution containing thiosulfate complex salt and thiosulfate metal complex salt. in contrast.

the tenn "carrier" does not refer to the mere suspension of materials like silver thiosulfate ioncomplexes in a base.Tlie term "carrier-free"refers to being without suchthings as carrier particles. porous particulate carriers. and the like used as carriersfor othermaterials For example.the compositions of the present Invention are "carrier-free" in thatthev comprise silver thiosulfate ion complexes that do not require such a carrier.

The term "base" refers to anv substance useful for the suspension of the silver thiosulfate ion complexes of the present invention. In a preferred embodiment. the base Is'anhydrous" (e.g., an ointment) and can be used to suspend a medicinal agent for topical administration. Usefulanhvdrous bases include. but are not limited to. whitepetrolatum.

AquaphorK ointment base, andpolyethylene glycol (PEG) polymers with molecular weights greater than 600. The preferred anhydrous base is a PEG ointment composition; an ointment made up of PEGs can absorb and associate with a small amount of water so that the water is not free to hydrolvze the thiosulfateligand. It should be noted that some water is tolerable in thefinal product but that, generally speaking. the presence of water will reduce the shelf-life of the composition. For example. an anhydrous base which contains no water and few. if any, hydroxy or acid groups should have a shelf-life of many years, while a base containing small amounts of water(c.g., less thant%) would have a shorter shelf-life(e.g., less than 6 months). If a PEG ointment base has averv small amount of water (e.g., much less than 1%), the silver thiosulfate ion complexes should be stable enough to provide the product with an acceptableshelf-life (e.g., greater than one year). In one embodiment. the base issemisolid

The term "silver thiosulfate ion complexes" refers to thesilver-containint, material produced by the process of the present invention and incorporated into the compositions of the present invention More specifically, the silver thiosulfate ion complexes are obtainedbv adding a silver halide.e.y., silver chloride. to an aqueous solution and thenadding athiosulfate salt. e.g., sodium thiosulfate, to the solution Though the benefit providedbv the complexes of the present invention is not limitedbv an understanding of the precise nature of the complexes. the chemical formula of theprimary silver thiosulfate ion complexes formed when a large excess of thiosulfate salt is used is representedbv [Ag(S2O3)3]5-Bv comparison. the chemical formula of the primary silver thiosulfate ion complexes formed when only a small excess of thiosulfate salt Is used is representedbv [Ag2(S2O3)3]4- Tile preferred silver thiosulfate ion complexes are those represented by [Ag2

(S2O3)3]4- The resulting silver thiosulfate ion complexes are In a relatively pure solid form, and are stable.

highly water soluble and antimicrobiallv active

The term "essentially anhvdrous silverthiosulfate ion complexes"refers to silver thiosulfate ion complexes thatmav be essentially free of all remnant water.i.e they mav contain a small amount of water (generally less than 5% of the original amount of waterpresent. preferably less than1 o. and most preferably less than 0 1%), provided that the water does not interfere with the antimicrobial function of the complexes

The term "suspended" refers broadly to the dispersion(i.e.. not dissolution) of material (e.g., silver thiosulfate ion complexes) in the base The material Ispreferablv finely divided andpref'erably dispersedhomogeneously throughout the base.

The term "aqueous solution" refers to a liquid mixture containing, among other things, water.

The term "solvent" refers to a liquid that is capable of dissolving a substance. The term "water-miscible solvent" refers to a solvent that is capable of being mixed with water and remaining so after completion of the mixing process.

The term "phase" refers to a physically distinct and separable portion of ahetero,eneous system. The term "biphasic separation" refers to the creation of two phases: generally speaking, a "biphasic separation" allows a material(e.g., silver thiosulfate ion complexes) to be partitioned into one of the resulting phases.therebv facilitating isolatio characteristics of the personal care product itself. The therapeutic composition may contain diluents.aduvants andexcipients. among other things.

The terms "subject" and "host" refer to humans and animals.

The term "approximatelv" refers to the actual value being within a range of the indicated value. In general. the actual value will be between 5% (plus or minus) of the indicated value.

The terms "topical." "topically." and the like include but are not limited to, thesurt'ace of the skin and mucosal tissue, in wounds. in the eves, nose. mouth, anus and vagina.

The term "wound" includes a burn, cut sore, blister. rash or any other lesion or area of disturbed skin. The term "wound dressing" includes foam dressings, thin film dressings, burn dressings, surgicaldressings. absorptive dressings, gauze. sheets or othertvpes of medical device used to treat wounds

The terms "microbe. "microbial," and thelike include bacteria. fungi, and viruses. The terms "antimicrobial" and "antimicrobial activitv" refer to theabilitv to kill or inhibit the growth of microbes.

The term "photostable" means that an object or material is resistant to discoloration when exposed to ambient light for a period of at least 7' hours.

The terms "matrix," "matrices" and the like reter broadly to materials inwhich the silver thiosulfate ion complexes of the present invention can be embedded in. attached to, or otherwise associated with A "polvmer matrix" is one type of matrix comprising one or more natural orsvnthetic compounds. usually of high molecular weight, in the formof repeatedlinked units The term "anhvdrouspolvmer matrix reters toaiiv solid material that mav be freeot water or that mav contain a small amount of water (generally less than 5% byweight).

provided that the water does not interfere with the antimicrobialfunction of the complexes carried by the matrix. The preferred anhydrous polymer matrix materials are materials compatiblewith the silver thiosulfate ion complexes of the present inventionTlie mostpreferred polymer matrix materials are those being compatiblewith the silver thiosulfate ion complexes and having somecapacitv to absorb and/or swell in the presence of water.

Examples of anhydrous polymer matrix materials. include. but are not limited to. adhesives such as acrylic-based pressure sensitive adhesives;biopolvmers such as silk; hydrocolloid materials such as sodiumcarboxvmethvicellulose. either alone orwhen bound in a polymer: andpolvmers such aspolvurethane in the form of coatings.films. foams. etc

The term "medical device" refersbroadlv medical implants. wound care devices, bodycavitv and personal protection devices, and the like.Medical implants include, but are not limited to, urinary and intravascuiar catheters. dialysis shunts. wound drain tubes. skin sutures.

vascular grafts and implantable meshes, intraocular devices, and heart valves. Wound care devices include, but are not limited to, general wound dressings, non-adherent dressings, burn dressings, biological graft

materials, tape closures and dressings, and surgical drapesFinallv, bodycavitv and personal protection devices include. but are not limited to, tampons, sponges, surgical and examination gloves, toothbrushes. intrauterine devices,diaphragms and condomsThe silver thiosulfate ion complexes of the present invention can be use to impart antimicrobial protection to objectsincluding, but notlimited to. medical devices

The term "purified" means that the material has been subjected to a process(e.g., extraction) to remove impurities. Following the process. the material mav be free from contamination of extraneous matter or. more commonly.onlv containimpurities at levels that do not Interfere with the intended function. For example, it is advantageous to produce silver thiosulfate ion complexes that do not contain significant amounts of waste salts(e.g., sodium nitrate or sodium acetate); if such waste salts are incorporated into compositions or medical devices. they mav be irritating to the skin or other tissue. In addition. they mav reduce the concentration of antimicrobiaily active silver. For example. if the silver thiosulfate ion complexes are made using silver iodide silver salt and sodium thiosulfate salt, the resulting waste salt would be sodium iodide. The iodide ion would aggressively competefor the dissociated ("free") silver ion. resulting In reduced concentrationof. antimicrobialiv active',i Iver DETAILED DESCRIPTION Oh THE INVENTION

The present invention relates to silver-based antimicrobial compositions. and processes tor making such compositions. that are suitable for use in the treatment and preventionof infections. In particular. the present invention relates to stable silver-based antimicrobial compositions. and processes for making such compositions. comprising carrier-free. suspended silver thiosulfate ion complexes in an a base, and silver thiosulfate ion complexes incorporated into ananhvdrous polymer matrix and used with a medical device.

The description of the Invention is divided into thefollowing pans:I) Processes To

Obtain Silver Thiosulfate Ion Complexes InA Solid Form;Ii) Compositions Containing

SilverTiliosulfate ion Complexes: III) Therapeutic Use Of Compositions Containing Silver

Thiosulfate Ion Complexes. and IV) Incorporation Of Silver Thiosulfate ion Complexes Into

Matnces For Use In Medical Devices. Each of these parts will be discussed in turn.

1. PROCESSES TO OBTAIN SILVER THIOSULFATE ION COMPLEXES

MATERIAL IN A SOLID FORM

As previously indicated. the compositions of the Oka Patent contain a thiosulfate salt.

at least one thiosulfate salt of a metal, and a porous particulate carrier The carrier was required because the thiosulfate salt and the thiosulfate salt of a metal can "hardly be obtained as a simple substance in a solid state" [Oka Patent, col.2 11. 45-46]. In contrast to the Oka

Patent. the present invention is directed at a process for obtaining carrier-free silver thiosulfate ion complexes Based on the prior art's acknowledgeddifficultv in obtaining silvertliiosulfate ion complexes in a carrier-tree solid state. the discovery of the process disclosed hereafterwas both surprising and unexpected.Nioreover. the process of the present invention also results in carrier-free silver thiosulfate ion complexes in high yields, another surprising and unexpected result

The present invention contemplates the production of carrier-free silverthiosuliate ion complexes wherein the ratio of thiosulfate ion to silver ion Is preferably at least 1 3 to I To optimize the antimicrobial effectiveness of the final products containing the silver thiosulfate ion complexes. it is preferable that the complexes be purified(2.,f'.n subjected to methods to remove contaminants such as waste salts in an amount that adversely interferes with the silver concentration obtainable)

The present invention provides two processes of producing purified silver thiosulfate ion complexes from thiosulfate ions and silver ions. The first process Is preferred when the ratio of thiosulfate ions to silver ions is greater than or equal to'-to-I and the second process

Is preferred when the ratio Is less than2-to-

A. Process For Producing SilverThiosullate Ion Complexes

Whell The Ratio Of Thiosulfate Ions To Silverlons Is

Greater Than Or Equal To 2-to-1

The process for producing essentiallyanhvdrous silver thiosulfate ion complexes when the ratio of thiosulfate

ions to silver ions is greater than2-to-1 involves four major steps The first step consists of making an aqueous solution of silverthiosuliate ion complexes. The aqueous solution of the silverthiosulfate ion complexes is obtainedbv first adding a silver halide. such as silver chloride. silver bromide. etc., to an aqueous solution. Thereafter. a thiosulfate salt. such as sodium thiosulfate or potassium thiosulfate, is added to the aqueous solution.

The use of a silver halide instead of anothersilver-containing molecule is preferred because the silver thiosulfate ion complexes produced are associated with increased short-termstabilitv. This is especially important when the concentration of the silver thiosulfate ion complexes is high and/or the ratio ofthiosult'ate ions to silver ions is low Likewise, the use of a silver halide promotesstabilitv when making a solution of the silver thiosulfate ion complexes when the concentration of silver thiosulfate ion complexes In theresulting aqueous solution is high. As indicated above.when making silver thiosulfate ion complexes where theprimarv silver ion complexes formed is representedbv the formula [Ag(S2O3)3]5-, the preferredproportions of thiosulfate salt to silver salt are equal to or greater than7 moles ot' thiosulfate saltfor Iniole of silver salt The most preferred proportionsof thiosulfate salt to silver salt are equal to or greater than3 -to- I

In making the aqueous solution of the silver thiosulfate ion complexes, the preferred silver halide is silver chloride. It should be noted that the silver chloride. as well as other silver halides. can be made in.lii In the aqueous solution In this'vav. a water-soluble silver salt such as silver nitrate or silver acetate is first dissolved in the aqueous solution. An equivalent or greater molar amount of a halide salt containing the chloride ion. such as sodium chloride, potassium chloride, and the like, Is then added. resulting In the precipitation of the silver chloride salt

'\ddditionally. inmaking the aqueous solution of the silver thiosulfate ion complexes. It is preferred that the concentrationof the initial silverhalide In the aqueous solution be less than 25 . Higher concentrations of the silver halide can lead to instability of the resulting silver thiosulfate solution; that is to say. the silver thiosulfate ion complexes within the solutionwill "break down" or decompose. leading to discoioration of the solution and precipitation of silver sulfide.

The second step in the process entails the additionof a solvent to the aqueous solution resulting from thefirst step to create a biphasic separation: in this way. the silver thiosulfate ion complexes separate into one phase.The preferred solvents are those which are watermiscible. Solvents such as ethvl alcohol,isopropyl alcohol. methyl alcohol. acetone.

tetrahydrofuran, and the like. are examples of solventswhich are useful incausing phase separation The solvent is added to the silver thiosulfate ion complexes solution in an amount such that the solution separates into two phases. During the formation of two distinct phases.

the silver thiosulfate ion complexes separate into one phaseTypically, the volume of the phase containing the silver thiosulfate ion complexes Isonlv a fraction(e.g., less than 20%) of the total volume of liquid; this denser liquid phase resembles a liquid mixture containing a heavy oil and an aqueous solution where the heavy oil accumulates at the bottom of the vessei containing the liquid mixture.

The phase containing the silver thiosulfate ion complexes is thought to consist of a high concentration(i.e., 50 - 70% of the total volume) of relatively pure silver thiosulfate ion complexes and water. Excess thiosulfate salts, waste salts, solvent. and other contaminants are thought to remain in the other (larger) phase of the biphasic solution.

In the third step, the separated phase containing the silver thiosulfate ion complexes can be collectedusing well known means. For example. the phase can be drawn up using a pipet and removedfrom the solution. Likewise. a separatorv tunnel can be used to separate the phase from the solution

After the liquid phase containing the silver thiosulfate ion complexes has been collected. the fourth step Involves treatment of the collected phase to create essentially anhydrous silver thiosulfate complexes. The silver thiosulfate complexes are purified.

containing insignificant amounts of waste salts(e.g., sodium nitrate or sodium acetate) and other extraneous materials. Treatmentswhich are useful include. but are not limitedto, evaporation. oven drying, freezedrying, solvent extraction. and the like. After the treatment.

the essentially anhvdrous silver thiosulfate complexes are ground into a fine powder.

B. Process ForPrOdllCillg SilverThiosll fate Ion (?oinplexes

When The Ratio OfThiosulfate Ions To Silver Ions Is Less

Than 2-to-I

The process for producing essentiallyanhvdrous silver thiosulfate ion complexes when the ratio of thiosulfate ions to silver ions is less than2-to-I Involves four major steps. The first step, making an aqueous solution of silver thiosulfate ion complexes. is analogous to the first step of the process where the ratio is greater than 2-to- I The malor difference of this process from that where the ratio is greater than 2-to-I Is that the second step of this process involves precipitation of the silver thiosulfate ion complexes from the aqueous solution (described below).

In the second step, a solvent is added to the aqueous solution of silver thiosulfate ion complexes to precipitate the silver thiosulfate ion complexes. The preferred solvents are those solvents which are water miscible. Solvents such as ethvl alcohol. isopropyl alcohol,methvl alcohol. acetone, tetrahydrofuran. etc., are examples of solvents which are useful in causing precipitation. The solvent Is added to the silver thiosulfate ion complexes solution in an amount such that the complexes precipitate.

In the third step. the silver thiosulfate ion complexes precipitate can be separated from the solution using anv standard.well-known technique. Filtration represents one preferredpreparation technique. The silverthiosuifate ion complexes are relativelv pure. containing insignificant amounts of waste salts (e.g., sodium nitrate or sodium acetate) and other extraneous materials like excess thiosulfate salts that are thought to remain in solution(i.e.

thev do not form a solid precipitate).

Following separation. the fourth and final step of removing essentially all remnant waterfrom the complexes from the collected phase creates essentiallyanhvdrous silver thiosulfate ion complexes. Methods which are useful include, but are not limited to, evaporation, oven drying, freezedrying, and the like After the treatment. the essentiallv anhvdrous silver thiosulfate ion complexes are ground into a tine powder

(v. TheN.ltllre Of Tlie Silver Thiosulfate Ion Complexes

While the benefit provided by the complexes of the present invention is not limited bv an understanding of the precise nature of the complexes, the solid material producedbv the two processes described above is thought to consist of a salt where the silverthiosultate ion complexes are represented by the formulas[Ag (S2O3)2]@-, [Ag(S2O3)3]@- [Ag2(S2O3)3]4 [Ag3(S2O3)4]5-, and similar complexes. Unexpectedly, it waswound that the form of the silver thiosulfate ion complexes produced Isverv dependent on the ratio of thiosulfate ion to silver ion

If the ratio ofthe thiosulfate ion to silver ion is low(i.e., less than2 1), silver thiosulfate ion complexes representedbv the formulas [Ag2(S2O3)3]4-, [Ag3(S2O3)4]5- and the like can be produced. The preferred silver thiosulfate ion complexes are those represented by [Ag2(S2O3)3]4-,which can be produced in accordance with thefollowing chemical equation:

3 Na2S2O3 + 2 AgCl# Na4Ag2(S2O3)3 + 2 NaCl

Conversely, if the ratio of the thiosulfate ion to silver ion is high (i.e., greater than2:1), relativelv pure silver thiosulfate ion complexes represented by the formulas [Ag(S2O3)2]3-, [Ag(S2O3)3]5- and the like can be produced.

The preferred silver thiosulfate ion complexes are those produced when the ratio of the thiosulfate ion to silver ion Is low. The purified silver thiosulfate ion complexes are carrierfree, photostable. highly water soluble. non-staining andantimicrobially active. This combination of features is not present in anv commercially available or previously described silver-containing composition.

II. COMPOSITIONS CONTAINING SILVER THIOSULFATE ION

COMPLEXES

Topical antimicrobial agents include therapeutic heavy metal compounds such assilver-containing compounds. Silver, in its ionic state(Ag), possesses a broad spectrum ofantibacterial antifungal, and antiviral properties and is relatively safe. Early studies showed that the silver ion Isoligodynamic. i.e., active at very low concentrations.[.\'ee generally,

Russellci al., Antimicrobial Activity and Action of Silver." Progress in MedicinalChemistry 31 351-70 (1994)]

The present invention is directed at, among other things, carrier-free silver thiosulfate ion complexescompositions Tlie provisionof carrier-free silver thiosulfate ion complexes Isidvantageous for at least two reasons. First, it providestlie ability tomake antimicrobialsliver thiosulfate ion complexes

compositionswithout the need for potentially irritating porous carrier particles. Second. It provides theabilitv to produce antimicrobial silver thiosulfate ion complexes compositions which can contain high concentrations of silver.resulting in compositions with potent antimicrobialactivitv

As set forth above, the carrier-free silver thiosulfate ion complexes are stable.

However. the complexes are not stable in allpharmaceutically-acceptable compositions

Indeed. it was found that the silver thiosulfate ion complexes decompose when incorporated

Into certain base compositions (See Experimental Section. infra). The decomposition of the silver thiosulfate ion complexes results in the silver-based composition bothchanging tol black color and losing antimicrobialactivitv. Given theinstabilitv of silver thiosulfate ion complexes when incorporated in certain base compositions. it was surprising and unexpected to discover silver thiosulfate ion complexes compositions which were, in fact, stable.

The stable silverthiosulfate ion complexes compositions of the present invention comprise carrier-free suspended silver thiosulfate ion complexes In a base. The preferred base

Is anhydrous. and in one embodiment the base is semisolid The stable silver-based compositions maintain their antimicrobial activitv.loreover. the amount of silver in the compositions can be varied over a large range of concentrations to provide compositions with different levels of antimicrobial potencv.

During the thirst step of the previously-described process for producingessentially anhvdrous silver thiosulfate ion complexes. an aqueous solution of the complexes is made. itshould be noted that aqueous solutionsot silver thiosulfate ion complexes can be added to an ointment or cream base to make an antimicrobial ointment or cream composition. in other words. a composition can be made after completing onlv the first of the four steps However.

the resulting antimicrobial ointment or cream composition suffers from two majordrawbacks.

First, the resulting silver thiosulfateloll complexes compositions will contain large quantities of excess thiosulfate salts as well as waste salts (e.g., sodiumnitrate. potassium nitrate. andpotassium acetate). When appliedtopically the antimicrobial composition containing these impurities may be Irritating The second major problem Is that ointment or cream compositions made with silverthiosulfate ion complexes fromsuch an aqueous solution are not stable forlong periods of time That Is to say. over a period of time theresult siiveBased antlmlcroblal compositions will turn black and loseantimicrobial efficacy

This destabilization occurs whether or not thesllver-based compositions are stored in an opaque container or a clear container Therefore. the destabilization Is not a photoseduction of the silver. Rather.that occurs is that the tliiosulfate ion component of the silver thiosulfate ion complexes experiences a chemical breakdown The effect of this chemical process is the breakdown of the silver thiosulfate ion complexes.

Again, while an understanding of themechanism involved Is not necessarv. it Is believed that the thiosulfate ionwhich makes up the silver thiosulfate ion complexes Istormed bv adding a sulfur atom to a sulfite ion in a complex reaction that can be summarizedbv the following chemical equation S + SO32- < S,O, The sulfur atom that is added to the sulfite ion togive S2O3@@ Issomewhat labile; thus, S2O32 may appropriately be represented asS-SO3@@ In aqueous solutions. thiosulfate decomposes over time. At moderately low pH levels the sulfur atom readily splitsoti: nominaliv yielding sulfur asfollows;

S-SO32- +H o S +HSO

While the acid decomposition of the thiosulfate ion nominally yields sulfur. it should be mentioned that veryfinely divided particles of sulfur in an acidic aqueous solution have the character of polysulfide ions. [Levenson. Complementary Processes (Ch 14), in The Theory of the Photographic process, Fourth Ed. MacMillan Publishing Co.. Inc.. New York (1977)]

As a result ofthe instability of the thiosulfate ion.when dissolved in water silver thiosulfate ion complexes also chemically decompose over time. It is believed that when the thiosulfate component of the silver thiosulfate ion complexes chemically breaks down, it releases silver ions which react with the released sulfur ions to form silver sulfide. Silver sulfide Is a black material having the molecular formula of Ag2S Due to silver sulfides high dissociation constant (pK = 49.1), silver sulfide is essentially non-antimicrobial. That is to say, the silver ion Is bound tightly to the sulfur ion so that It can only ionizeverv slowly from the silver sulfide salt. As a result. little. If any, ionized silver is available to provide antimicrobial activity

Likewise. silver thiosulfate ion complexes. when added to either an ointment base which contains a small proportion of water or awater-containing cream base in order to form an antimicrobial composition.will

decompose over a relatively short period oftine. Tie resulting antimicrobial composition will turn black as the silver thiosulfate ion complexes in the composition decompose to silver sulfideAdditional lv. the compositionwill lose Its antimicrobial efficacy with decomposition of the silver thiosulfate@on complexes.

In contrast, the previously described four-step process for producing essentiallyanhydrous silverthiosulfate ion complexes allows the productionof compositions that are stable over long periods of time. The stable silver thiosulfate ion complexes compositions of this invention comprise carrier-free suspended silver thiosulfate ion complexes in a base. The baseswhich are most useful forthe present invention entail anv compound or mixturewhich is capable of suspending the coniplexes. Preferably, the ba

The methods for suspending the purified silver thiosulfate ion complexes, In the form of a fine powder, into a base to form a silver-based antimicrobial composition are well known in the art. For example, one method involves heating the base until it has liquefied; then, while the base cools.adding the silver thiosulfate ion complexes and stirring until the base has resolidified. This method produces a suspension of the silver thiosulfate ion complexes within the base, preferably a homogeneous suspension.

The concentration of the silver thiosulfate ion complexes within the base is such as to provide antimicrobialactivitv The preferred concentration of the silverthiosuliate ion complexes Is0.1% to3.0 ,/e However, silver thiosulfate ion complexes concentrations can range up to 10% to 30% depending on the antimicrobialpotencv required. The most preferred concentration Is between 0.2% and I 5%.Generally speaking, the effective concentration is that concentrationwhich is higher thanthe minimum inhibitorv concentration tor a particular microbe .\s would be expected. certain microbes are more sensitive to silver than other microbes,e.g., gram (-) microbes are generally more sensitive than gram (+)microbes As a result. a concentration less than 01% could be effective depending on the microbe and the intended use of the final product.

The resulting silver thiosulfate ion complexes compositions of the present invention are antimicrobially active and stable when compared to compositions that use bases which are notanhydrous Additionally, the silver-based antimicrobial compositions of this invention show no photo-discoloration when exposed to ambient room light over a72 hour period.

Though the compositionsmust be in ananhvdrous base in order to maintain their stability. it is not intended that the compositions of thepresent invention be Limited bv theparticular nature of the therapeutic preparation For example. the present invention contemplates compositions that include physiologically tolerable diluents.adiuvants andexcipients. such as pharmaceutical grades of mannitol. lactose. starch. magnesium stearate.

sodiumsaccharin cellulose. magnesium carbonate. and the like. These compositions typically contain 1%-95% of active ingredient, preferably 2%-70% In addition, if desired the compositions may contain minor amounts ofauxiliarv substances such as stabilizing or pH buffering agents or preservatives

III. THERAPEUTIC USE OF COMPOSITIONS CONTAINING SILVER

THIOSULFATE ION COMPLEXES

The silver thiosulfate ion complexes compositions of the present invention can be used topically for example, on skin, in wounds in the eyes, nose. and mouth, in the treatment and prevention of infection. As alluded to above, the compositions are effective against bacteria.

viruses. and fungi. For example.A. coli and many species of Klebsiella, Proteus, I'sendomonas, Staphylococcus. and Candida mav be inhibited or killed by the compositions of the present invention. In general. the dosage required for therapeutic efficacy willvarv according to the microbe involved. the type of use and mode of administration, as well as the particularized requirements of individual hosts.

The therapeutic preparations can be administered for clinical use in humans and forvetennary use. such as with domestic animals. In manners known In the art and similar to other therapeutic agents. Though not limited to any particular means of application. the antimicrobial compositions can be applied using gloved hands orbv an applicator. Likewise.

the antimicrobial compositions can be applied to the surface of a dressing, which can then be applied topically Ophthalmic infections can be treated using standard procedures in the art.

such asbv pulling down the lowereyelid to form a pocket and applying the composition thereto By way of furtherillustration. infections of the mouth can be treatedbv applying the composition with a sponge applicator or a toothbrush

Bacterial resistance to silver is known to occur in certain situations, more specifically.

@scherichia coli and Salmonella typhimurmm are known to develop plasmid-encoded resistance to silver. [Russell et al., Progress inMedicinal Clemistry 31 351-70 (l994)J Two related methods are commonlv used to prevent and combatdrug resistance

The first method entails the combination of two ormore therapeutic agents intol final composition. For example. the ss-lactamase inhibitor clavulanate potassium has been added toamoxicillin. resulting in a combination preparation (AugmentinTM: SmithKline Beecham) with expanded antimicrobial activitywhile clavulanic acid has onlyweak antibacterialactivitv when used alone. its combination with amoxicillin results in a synergistic effect.

The second method entails the concomitant administration of two or more distinct antimicrobial agents.This method is based on the principle that a microbe that is resistant to one agent mav be susceptible to another. This is especially important. e.g., in tuberculosis.

which is caused by Mycobacterium tuberculosis Particular M.@uberculosis bacteria that cause tuberculosis are known to displav resistant to each of theprimarv therapeutic agents. As a result. treatment oftubercuiosis often requires combinations of three or more drugs forperiods exceeding one vear. [See Doolv et a/, al." N1ultidru'-resistant tuberculosls," Ann. Int.

Med.117.257-59 (1992); Nadler "Multidrug resistant tuberculosis" N Eng. J. Med.

327:1172-75 (1992)].

The present invention contemplates combining a topical silver-containing preparation with another medicinal agent to form a pharmaceutical composition. Indeed, the present

Invention contemplates the use of manv diverse medicinal agents. including antimicrobial agents. topically active drugs, andsystemically active drugs. The preferred medicinal agents contemplated for use in the pharmaceutical compositions of the present invention are those that can be used as antimicrobiai agents in the treatment and prevention of infection and disease. Suitable antimicrobial agentsinclude, but are not limited to. penicillin, tetracychne, oxvtetracvcline. chlortetracvcline. chloramphenicol. chlorhexidine.mupirocin. metronidazole.

miconazole,acyclovir. itraconazole and sulfonamides .\dditional antimicrobial agents include antimicrobial peptides such as magainins, cecropins.proteins bacteriocins and defensins.

The pharmaceutical compositions of the presentInvention possess an additional broad spectrum of antimicrobial protection by combining antimicrobial medicinal agents in a stable fashion with silver thiosulfate ion complexes Furthermore. as previously indicated, the use of silver thiosulfate ion complexes with an antimicrobial medicinal agent mav aid in preventing the formation ofdrug-resistant microbes. Moreover. since silver ions are oligodynamic and are notimmediatelv exhausted(i.e.. thev have along-lasting or "residual" effect). the presenceot silver ions in the pharmaceutical compositions results In compositionswhich are longer lasting than those containing a single antimicrobial agent

Medicinal agents besides antimicrobial agents are also contemplated for use in thepharmaceutical compositions of the presentinvention. iiicluding topically active drugs for the treatment of diseases Suitable topicallyactive drugs Include. but are not limited to. acne preparations such as isotretinoin, benzoyl peroxide, salicylic acid and tetracycline, anesthetics tor topical administration such as dibucaine. lidocaine. benzocaine. tetracacine.deperodon and1)ramoxine hydrochloride;anti-intlammatory agents such as betamethasone benzoate.

betamethasone valerate. desonide. fluocinolone acetonide.halclnonide. hvdrocortisone: antiperspirants and medications used in the treatment of hyperhidrosis such as glutaraldehyde, methenamine, glycopyrrolate, scopolamine hvdrobromide; antipruritic and external analgesic agents such as camphor. menthol. salicviic acid. methvlsalicvlate; cieansing agents such as soaps and shampoos; keratolytic, cytotoxic, and destructive agents such as anthralin.

cantharidin, fluorouracil, podophyllotoxin, resorcinol; and pigmenting and depigmenting agents. sunscreens such as hydroquinone, monobenzone. trioxsalen and p-aminobenzoic acid, anabolic steroids for building up tissues under wound healing such as methandienone;proteolytic agents for the decomposition of fibrin such as trvpsin; vasodilating substances for

Improving the flow of blow during wound healing such as tolazoline: thrombosis-hampering substances such as heparin: certainbiologicallv active substances which affect tissue formation and tissue stabilization such as ascorbic acid and EGF (epidermal growth factor), EGF-URo (EGF-urogastron). somatostatin. somatotropin asellacnne. and TGF: andmucolvtic and antiviral medicaments which are globulins such

aslysozyme

A pharmaceutical composition with a broad spectrum of antimicrobial protection is produced by combining one or more topically active drugs in a stable fashion with a pharmaceutical composition containing silverthiosulfate ion complexes. In situations where the topicallv active drugs are used to treat a disease which has an abundance ot' dead tissue(c.g.. a fungating tumor or a decubitus ulcer), the additionof antimicrobial silver ions will aid in the prevention of asecondarv infection at the diseased site. Furthermore, the presence of ionized silver in the pharmaceutical composition can aid in the prevention of malodor caused by anaerobic and aerobic microbes at the diseased site. Finally. combining a topically active drug with the silver thiosulfate ion complexes minimizes the need to apply additional topical antimicrobial compositions which may be incompatible with the medicinal agent. resulting in both time and cost savings.

In addition to medicinal agents which are antimicrobial agents ortoplcallv activeagents. the present invention also contemplates the useof svstemlcallv activedrugs in the pharmaceutical compositions of the present inventionThe systemically active drugs are absorbed bv the bodv surface when applied topically, either neat orwith the aid of a solvent.

Suitable systemically activedrums include. but are not limited to. sedatives andhypnotics such as pentobarbital sodium, phenobarbital, secobarbital sodium. carbromal. and sodium phenobarbital; psychic energizers such as 3-(2-1-aminopropyl)-indole acetate and 3-(2aminobutyl)-indole acetate: tranquilizers such as reserpine. chlorpromazinehvdrochloride. and thlopropazate hydrochloride; hormones such as adrenocorticosteroids.for example,6-a- methylprednisolone, cortisone, cortisol, and triamcinolone: androgenic steroids, for example.

methyl-testosterone, andtluoxvmesterone: estrogenic steroids. for example.oestrone,

17ss-estradiol and ethinylestradiol: progestational steroids, for example17-α- hydroxyprogesterone acetate, medroxyprogesterone acetate, 19-norprogesterone, and norethindrone: and thvroxine; antipyretics such as aspirin.salicylamide, and sodiumsalicylate: antispasmodics such as atropine. methscopolamine bromide. and methscopolamine bromide with phenobarbital; antimalarials such as the 4-aminoquinolines, 8-aminoguinolines, andpyrimethamine, and nutritional agents such as vitamins. essential amino acids. and essentialfats

A pharmaceutical composition with a broad spectrum of antimicrobial protection is producedbv combining one or moresystemically activedrums tn a stable fashion with silver thiosulfate ion complexes. The addition of silver thiosulfate ion complexes with one or moresystemically active drugs to produce a pharmaceutical composition assists in the preservation of the pharmaceutical compositionbv protecting it from microbial proliferation and overgrowth, which could otherwise lead to spoilage of the medicinal composition containing the systemically active drugs.

Finally, the antimicrobial compositionsmay beuseful in makinginfection-resistant cosmetics and personal care productsIV. INCORPORATION OF SILVER THIOSULFATE ION COMPLEXES

INTO MATRICES AND THE USE OF SUCHNIATRICES

This section describes the incorporation of silver thiosulfate ion complexes inton1atrices. mostpreferably anhvdrous polymeric matrices In turn. the matrices products can be used in conlunction with medical devices for the treatment and prevention of infections and diseases. In general. the silver thiosulfate ion complexes can be incorporated into the

polymer matrix either(l) during the production of the polymer matrix' or (li)after the polymermatrix has been produced It Is most preferred that thecomplexes arehomogeneously dispersed in the matrix

A. The Nature of Silver Thiosulfatelon-Containing Anhydrous Polvmeric Matrices

Similar to the situation described above regarding compositions. aqueous solutions of silver thiosulfate ion complexes which have not been purified can be incorporated intopolymer matnces to render the matrices compositions antimicrobial. However. the resulting matrices compositions will contain large quantities of excessthiosulfate salts as well as waste salts such as sodium nitrate, potassium nitrate. potassium acetate, etc.As set forth above.

these impurities mav be irritating when the matrices compositions are appliedtopical lav

Furthermore. the presence of the waste salts may have a negative Impact on the physical characteristics (e.g, feel.strength, and stiffness) of the final matrices compositions.

The purified carrier-free silver thiosulfate ion complexes of this invention can be incorporated into

ananhvdrous polymer matrix to produce photostable antimicrobial matnces compositions: these compositions are useful in making medical devices. The present invention contemplates that any solid material that does not contain a significant amount of water mav be used as an anhydrous polymer matrix The preferredanhvdrous polymer matrix material is anv material that Is compatible (i.e., does not contain reactive components which could lead to the destruction of the thiosulfate ligand,therebv destabilizing the silver thiosulfate ion complexes) with the silver thiosulfate ion complexes of this invention. The most preferred polymer matrix material is one that is compatible with the silver thiosulfate ion complexes of this invention and has some capacity to absorb and/or swell in the presence ofwater: tlie ability of the polymermatnx to absorb andiorswell in the presence of water assists in the dissolution and diffusion of the silver thiosulfate ion complexes from the polymer matrix

It should be noted that the silver thiosulfate ion complexes of the present invention can be used withanhvdrous polymer matrices which do have reactive components as long as the media Is such that the reactive chemical component of the polymer matrices cannot react with the silver thiosulfate ion complexes. For example. when incorporated into a solution of alginate material (which contains a number of chemical reactive groups such ascarboxylic acid). the silver thiosulfate ion complexes of the resulting composition are unstable over long periods: the water in thesolutlon acts as a media inwhich the reactive groups of the alginatematerials can destabilizethe silver thiosulfateloll complexes However. when the alginatematerial lsdry. the silver thiosulfate ion complexes remain stable

Anhydrous polymer matrixmaterials useful in this invention include. but are not limitedto. the following: adhesives such as acrvlic-based.pressure-sensitive adhesives: biopolymers such as silk. alienatematerials. etc., hvdrocolloid materials such as sodium carboxymethylcellulose. either alone or when bound in apolymer; polvmers such as polyurethane, silicone. etc. in the form of coatings, films or foams. and the like. Theseanhvdrous polymer matrix compositions can be used alone or as a component of another material. such as a medicaldevice.

The concentration of the silver thiosulfate ion complexes within theanhvdrous polvmeric matrix should be such as to provide antimicrobialactivitv. The preferred concentration of the silver thiosulfate ion complexes in the finalpolvmeric matnx is0 1% to3.0% However. silver thiosulfate ion complexes concentrations can range up to 10% to 30%, depending on the antimicrobialpotencv required and thepermcabilitv of thepolvmeric matrix.

The most preferred concentration is between 0.2% and I 5% The resulting silver thiosulfate ion complexes-containing matrices compositions of this invention are antimicrobially active and stable.Additionally, the compositions of this invention show no photo-discoloration when exposed to ambient room light over a 72-hour period.

It should be noted that the silver thiosulfate ioncomplexes-containing matrices compositions of the present invention can be used alone in the treatment and prevention of infection in a manner analogous to the compositions described above Moreover. as previously alluded to, the matrices compositions can be used to make medical devices such as dressings. tamponades. etc.which can be used in the treatment and prevention ot'infection

B. IncorporationDuring Production OfPolvmer Matrix

The method of incorporating the silver thiosulfate ion complexes during the production ot thepolymer matnx itself will be dependent on the production process for that polymer matrix The methods of incorporationfor several polymer matrices follows Of course.

deviations from these methods as well as the use of different matrices than those specifically mentioned are within the scope of the present invention

The first method of incorporation is useful if the polymer matrix is produced from a solvent solution of polymer matrix material In this situation. thesilver thiosulfate ioncomplexes in a solid powder form can be added to that solution and mixedthoroughly @. ponchmlntltlon of the solvent through standard means in the art. the remainingpolvmer matrixmaterial will have the silver thiosulfate ion complexes dispersed.preferably tulle complexes are dispersedhomogeneously. For example. in an adhesive material dissolved in a solvent, the silver thiosulfate ion complexes in a powder form arethoroughly mixed In The mixture Is then coated on a liner and dried The resulting adhesive film has the silver thiosulfate ion complexes incorporated as a dispersion.

Another method of Incorporation Is useful if the production process for the polymer matrix involves the use of water as a solvent.(i.e., latex polymer svstems. solvent extraction svstems) or as a reactant (i.e.,polvurethane foam production.alginate tiber production.etc.).

With this method. the silver thiosulfate ion complexes can be dissolved in the water prior to the production

process To illustrate. If a polymer film Is being producedbv coating with a polymer latex solution. the silver thiosulfate ion complexes can be added directly to the latex solution Once added. the silver thiosulfate ion complexes will dissolve. After coating anddrying, the resulting polymer film will have the silver thiosulfate ion complexes homogeneously dispersed in the film.

Likewise. in producing apolvurethane foammatrix bv reacting the polyurethaneprepoivmer with water. the silver thiosulfate ion complexes can be dissolved in the water prior to reacting it with theprepolvmer. After the polyurethane foam has reacted and been dried. the silver thiosulfate ion complexes will be dispersed throughout the foam matrix.

Additionally, in producing a water insoluble alginate materialbv reacting an alginate solution with an aqueous calcium chloride bath, the silverthiosuliate ion complexes can be dissolved in either the water making up thealitinate solution or the calcium chloride bath.

The alginate solution. when extruded into the calcium chloride bath. will result in crosslinked alginate fiberswhich incorporate the silverthiosulfate ion complexes Upondriving of these fibers. the silver thiosulfate ion complexes will be dispersed throughout the alginate matrix

Another method of Incorporation can be used in coniunction with the production ofpolymer matrices such as a hydrocolloid matrix made upot' a hvdrocolloid material(e.,L,., carboxymethylcellulose) in a polymer binder in this situation. the silver thiosulfate ion complexes. in a solid form. can be mixed directly with the hvdrocolloid material prior to the production process. Likewise. the silver thiosulfate ion complexes can be dissolved in waterwhich is then used to treat the hvdrocolloid material so that the solution is absorbedbv the hydrocolloid material and then dried Thereafter. the treated hvdrocolloid material Isprocesses using standardprocedure to produce the hvdrocolloidpolvmer matrixwhich contains the silver thiosulfateion complexes dispersed in the hydrocolloid component of thematrix

C. Incorporation After Production Of Polymermatrix

In addition to incorporation prior to or during the production of the polymer matrix.

silver thiosulfate ion complexes can be Incorporated after the polymer matrix has been produced. One approach is to form an aqueous solution of the silver thiosulfate ion complexes and then apply this solution to the finishedpolymer matrix. This silver thiosulfate ion complexes solution can be applied to the polymer matrixbv spraying. dipping, painting or other suitable means.

Bv wav of illustration. an aliquot of the silver thiosulfate ion complexes can be applied onto and absorbed into a finished foamdressing ter drving, the silver-based foam composition will be stable and antimicrobial. Likewise. the silver thiosulfate ion complexes solution can be sprayed on the surface of a polymer or adhesive film which, after drying, will be stable and antimicrobial.

D. Precautions During Incorporation

Regardless of the method of incorporating the silver thiosulfate ion complexes with thepolymer matrix, certain precautions need to be considered. First. if incorporation of the silver thiosulfate ion complexes into thepolvmeric matrix involves the use of water, it is very

Important that the water be removed from thepolymeric matrix If the water is not removed.

the silver thiosulfate ion complexes will become destabilized within the polymeric matrix over time

Second. though the water can be removed using anv standard method. if the water is removedbv drying the polymeric matrix In an oven. care should be taken to use only moderate temperatures. temperatures of 20 C to 700C may be used.while temperatures of300C to 500C are preferred If the temperature becomes too hot. rapid destabilization of the silver thiosulfate ion complexes can occur.

Finaliv.when the silver thiosulfate ion complexes are in solution. contact withmetal surfaces should be avoided. The silver thiosulfate ion complexes soluti

BASF (BASF Corp., Chemical Division: Parsippany,NJ); Belersdorf Inc. (BDF Plaza

Norwalk. CT); Columbus (Columbus Chemical Industries: Columbus. WI); Cook Composites andPolvmers (KansasCitv, MO); Difco (Difco Laboratories, Detroit, MI); Hampshire (Hampshire Chemical Co.. Lexington,MA); Johnson & Johnson Medical, Inc. (Arlington,Tx), Owen Laboratories (San Antonio. TX); Protan (Drammen, Norway); Roundy(Roundv's

Inc.. Milwaukee, WI); Sigma (Sigma Chemical Company, St. Louis. MO); SmithKline

Beecham (Philadelphia. PA); Steriseal (Steriseal Ltd, England); Whatman (Whatman

International Ltd.,Enrland): WOHL (Wisconsin Occupational Health Laboratory,Madison,

WI).

The following examples serve to illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof. The experimental disclosurewhich t'ollows is divided into: I) Processes To Obtain SilverTliiosulfate Ion Complexes: II) Compositions Containing Silver Thiosulfate Ion Complexes;

III) AntimicrobialActivitv Of Compositions Containing Silver Thiosulfate Ion Complexes:

IV) Use Of Silver Thiosulfate ion Complexes in Medical Devices, and V) Use Of Silver

Thiosulfate Ion Complexes in Combination With Other Medicinal Agents.

I. PROCESSES TO OBTAIN SILVER THIOSULFATE ION COMPLEXES

EXAMPLE I

ProcessFor Making Silver Thiosulfate IonComplexes Using Silver

Chloride When The Ratio Of Thiosulfate Ions To Silver Ions Is Greater Than 2-to-1

This example illustratestlie process for producing silver thiosulfate ion complexes when the ratio of thiosulfate ions to silver ions is greater than2-to-I Thatis. a biphasic separation is employed in this example.

The silver thiosulfate ion complexes were producedbv first making a silver chloride precipitate in an aqueous solution (hereafter. "silver chlorideprecipitate/aqueous solution")

The silver chloride precipitate/aqueous solution was madeby mixing 20 ml of a silver nitrate (Aldrich; deionized water as the diluent) solution (I mmol/inl) with22 ml of a sodium chloride solution (I mmol/ml) (Aldrich; deionized water as the diluent) in a 500 ml separatorv tunnel. To the resulting silver chloride precipitate/aqueous solution was added 60 ml of asodium rhiosulfate (Columbus: deionized water as the diluent) solution (I mmol/ml) Tie resulting mixture was agitatedbv shaking the separatorsfunnel until all of the silver chloride precipitate was dissolved.

The silver thiosulfate ion complexes produced were separated by adding200 mi of ethvl alcohol to the container. Upon addition of the ethyl alcohol. the solution became cloudy and separated into two separate phases. The two phases were separated using the separatorv funnel. The weight of the material in the phase containing the silver thiosulfate ion complexes was approximatelv 17 g. This phase was then treated by adding 70 ml ethvl alcohol and 40 ml of acetone to make the silver thiosulfate ion complexes essentiallyanhvdrous After sitting overnight. the silver thiosulfate ion complexes were in the form of a pure. white solid material in the bottom of the container Thereafter, the solvent was decanted and the white solid was dried in an oven (62 C) and ground to a fine white powder using a monar and pestle. The weight of the dried silver thiosulfate ion complexes was 10 03

The silver thiosulfate ion complexes wereanalvzed for silver. sodium and sulfur usingInductivelv Coupled Plasma Arson Emission Spectrometry The analvsis. performed by

Wisconsin Occupational Health Laboratory (WOHL), included measurement of the amount of silver using a method based on NIOSH S182. Brieflv. a representative portion of the silver thiosulfate ion complexes was weighed and diluted 1/1000 in a dilute nitric acid solution

Thereafter. an aliquot of the sample wasanalvzed (JarrelASH ICP: Franklin,MA); theanalvsis gave the following results (expressed as percentages of the air dried samples)

Silver 20%

Sodium 17%

Sulfur 32%

The results of theanalvsis suggest that the silver thiosulfate ion complexes wererelativelv pure and corresponded to the formula Na4H[Ag(S2O3)3] (Silver:20.1 1% (w/w).

Sodium: 17 13% (w/w), Sulfur 35 75% (w/w))

The calculated vield of silver thiosulfate ion complexes using the process of this example Is 937 e

EXAMPLE 2

Process For Making Silver Thiosulfate Ion Complexes Using Silver

Chloride When The Ratio Of Thiosulfate ions To Silver Ions Is Equal To2-to-I

This example illustrates the process for producing silver thiosulfate ion complexes when the ratio of thiosulfate ions to silver ions is equal to 2-to-1 The silver thiosulfate ion complexes were isolated through the use of a biphasic separation

In this example, silver thiosulfate ion complexes were producedbv first making a silverchloride precipitate in an aqueous solutionbv mixing 10ml of a silver nitrate (Aldrich; deionized water as the diluent) solution (1 mmol/ml) with 10 ml of a sodium chloride (Aldrich; deionizedwater as the diluent) solution (I mmol/ml) in a 100 ml specimen container To this silver chloride precipitate/aqueous solution was added 20 rnl of a sodium thiosulfate (Columbus. deionized water as the diluent) solution (Immoliml) Tulle result mixture was agitatedbv shaking the container until all of the silver chloride precipitate was dissolved.

Thereafter. the silver thiosulfate ion complexes were separatedbv adding 50 ml of acetone to the container. Upon addition of the acetone. the solution becamecloudv and separated into two separate phases. Thetwo phases were separated into individual containers using a pipet. The phase containing the silver thiosulfate ion complexes was treatedbv adding50 ml of acetone to make the silverthiosultate ion complexes essentially anhydrous

After sittingovernight. the silver thiosulfate ion complexes were in the formof a purewhite solid material Thereafter. the solvent was decanted andtlie white solid was dried in an oven (62 C) andround to a fine white powder using amortar and pestle. Theweight of tile dried silver thiosulfate ion complexes was 3.97 trams

The resulting silver thiosulfateloll complexes materialwas analvzed for silver. sodium andsulfur using anInductivelv Coupled Plasma (ICP; described above) Theanalvsis gave the following results

Silver 25%

Sodium 17%

Sulfur 30%

The results of theanalvsis indicate that the silver thiosulfate ion complexes were relatively pure corresponding with the followiny theoretical formula:Na3[Ag(S2O3)2]#2H2O (Silver 24 7% (w/w), Sodium. 15.78% (w/w), Sulfur; 29 3% (w/w)).

The calculated vield of making silver thiosulfate ion complexes using the process of this invention is 90.8%

EXAMPLE 3

Process For Making Silver Thiosulfate Ion Complexes Using Silver

Chloride When The Ratio Of Thiosulfate Ions To Silver Ions Is Less Than 2-to-I

This example further Illustrates the process for producing silver thiosulfate ion complexes when the ratio of thiosulfate ions to silver ions Is less than 2-to-1 As in thepreceding example. the silver thiosulfate ion complexes were Isolatedthrough the formationot a precipitate rather than a biphasic separation.

In this example. silver thiosulfate ion complexes were madebv first making a silver chloride precipitate in an aqueous solution by mixing 10 ml of a silver nitrate (Aldrich; deionized water as the diluent) solution (Immol/ml) with '0 ml of a sodium chloride (Aldrich. deionized water as the diluent) solution(I mmol/ml) in a 100 mlspecimen container. To this silver chloride precipitate/aqueous solutionwas added 15 ml of a sodium thiosulfate (Columbus: deionized water as the diluent) solution (1 mmol/ml). The resulting mixturewas agitatedbV sl1akinlS the container until all ot' the silver chloride precipitatewas dissolved

Thereafter,the silver thiosulfate ion complexes were precipitated from the solution bv adding50 ml of acetone tothe container The precipitated silver thiosulfate ioncomplexes were in the formof a pure white solid

material. The solvent was decanted and the white solid was dried in an oven (620C) and ground to a fine white powdertising a mortar andpestle

The silver thiosulfate ion complexes were analyzed tbr silver. sodium and sulfur using anInductiveiv Coupled Plasma(ICP. described above) Tlieanalvsis gave the following results:

Silver 32%

Sodium14%

Sulfur 29%

The results of the analysis indicate that the silver thiosulfate ion complexes wererelativelv pure corresponding with the following theoretical formulaNa4[Ag2(S2O3)3]#H2O.

(Silver: 32.6% (w/w), Sodium: 13.9% (w/w), Sulfur: 29.0% (w/w)).

EXAMPLE 4

Process For Making Silver Thiosulfate Ion Complexes Using SilverBromtde

In making the aqueous solution of silver thiosulfate ion complexes. the preferred silver halide is silver chloride (Examples 1-3), this example illustrates that other silver halides mav be used.

In this example,tlie silver thiosulfate ion complexes were producedbv first making a silver bromide precipitate In an aqueous solution (hereafter. "silver bromide precipitate/aqueous solution")bv mixing2 ml of a silver nitrate (Aldrich. deionized water as the diluent) solution(I mmol/ml)with 2.2 ml of a sodium bromide (Aldrich: deionized water as the diluent) solution (1 mmol/ml) in a50 ml beaker. To this silver bromide precipitate/aqueous solution was added 6 0 ml of a sodium thiosulfate (Columbus. deionized water as the diluent) solution(I mmol/ml)The resultingmixture was agitatedby stirringuntil all of the sodium bromide precipitatewas dissolved

The silver thiosulfateioii complexes were separated bv adding 20.0 ml of acetone tothe containerUpon addition ofthe acetone. the solution separated into two phases Thephase containing the silver thiosulfate ion complexes was collected and treatedbv adding 7 0ml ethvl alcohol and 4.0lnl of acetone to make the silver thiosulfate ion complexesanhvdrous. Alter sitting overnight. the silver thiosulfate ion complexeswere In the fonn ofa white solid material at the bottom of the container.Tulle solvent was decanted and the white solidwas dried in an oven (62 C) and ground to a tinewhite powder using amortar andpestle The resulting weight of the dried silver thiosulfate ion complexes was0.88 g.

EXAMPLE 5

Process For Making Silver Thiosulfate

Ion Complexes Devoid Of A Phase Separation Procedure

To illustrate the Importance of making silver thiosulfate ion complexes using the processes of this invention silver thiosulfate ion complexes were made by a process which did not use a phase separation procedure when the ratio of thiosulfate ions to silver ions is greater than2-to-l

This comparison process was performed by first making a silver chloride precipitate in an aqueous solution (hereafter, "silver chloride precipitateiaqueous solution") by mixing2 ml of a silver nitrate (Aldrich; deionized water as the diluent) solution (1 mmol/ml) with2.2 ml of a sodium chloride (Aldrich: deionized water as the diluent) solution (1mmol/ml) in a50 inl beaker. To this silver chlorideprecipitatelaqueous solution was added 6.0 ml of a sodiumthiosulfate (Columbus: deionizedwater as the diluent) solution < I mmol/ml) The resulting mixture was agitatedbv stirring until all of the sodium chloride precipitatewas dissolved.

The resulting silver thiosulfate ion complexes solution was placed In a convection oven at 62 C overnight to evaporate the water.Tlie solidmaterial produced had asplotchy tan color with areas which had a deep brown color. The lack of a pure white solid indicates that this process leads to abreakdown or decompositionof silver thiosulfate ion complexes

II. COMPOSITIONS CONTAINING SILVER THIOSULFATE ION (:oMPLIEXES

EXAMPLE 6

StableAntimicrobial Composition - PEG Base

The previous examples were directed at processesfor making silver thiosulfate ion complexes. This example, as well as Examples7-9 that follow. compare vanous antimicrobial compositions containing the silver thiosulfate ion complexes. In this example. a silver-based antimicrobial composition was produced in a PEG base. Specificallv.40 g ot apolvethvlene glycol (PEG) base (PEG 600:PEG 1000 = 0 3 0.7, Aldrich) was melted. While cooling, 0.47 of the silver thiosulfate ion complexes of Example I were stirred into the melted PEG baseThe stirring was continued until the silver thiosulfate ion complexes were homogeneously suspended. While stirring,the melted PEG/silver thiosulfate ion complexes composition was cooled to produce a semisolid base. The amount of silver in this silverbased antimicrobial composition was equivalent to0.5 0 silver nitrate.

EXAMPLE 7

Stable Antimicrobial Composition -Aquaphor@

To further Illustrate a silver-based antimicrobial composition of this invention, 402 of

Aquaphor Cholesterolized Absorbent Eurcerite Ointment Base was melted.Aquaphor@ is aunable, neutral. odorless,anhvdrous ointment base (Belersdorf Inc)While cooling, 1.26 g of the silver thiosulfate ion complexes of Example I were stirred into the melted Aquaphor"base. The stirring was continued until the silver thiosulfate ion complexes were homogeneously suspended. While stirring, the meltedAquaphor@/silver thiosulfate ion complexes composition was cooled to a semisolid base The amount of silver In this silverbased antimicrobial composition was equivalent tol .O',o silver nitrate.

EXAMPLE 8

Stable Antimicrobial Composition - White Petrolatum USP

To illustrate an alternative silver-based antimicrobial composition of the present invention. 40g of white petrolatum USP (Roundv's Pure PetroleumJellv White PetrolatumSP) was melted While cooling. 2.52 g of the silver thiosulfate ion complexes of Example Iwere stirred into themelted white petrolatum base. Tlie stirring was continued until the silver thiosulfate ion complexes were homogeneously suspended While stirring, the melted white petrolatum/silver thiosulfate ion complexes compositionwas cooled to a semisolid base.The amount of silver in this silver-based antimicrobial composition was equivalent to2.00/0 silver nitrate.

EXAMPLE 9

Stability OfAnhvdrous AndHvdrated Antimicrobial Compositions

This example illustrates theinstabilitv ofhvdrated sllver-based antimicrobial compositionscomprising silver thiosulfate ion complexes.The experiments of this example utilize the compositions produced in Examples6-8. as well as a composition containing a different base.Velvachol@ Cream.

EXAMPLE 9A

PEG Base Plus Water

A hydrated siiver-based antimicrobial composition was made where the composition base was PEG. The composition was madebv mixing 9 g of the silver-based antimicrobial composition of Example 6 with I ml of water. This silver-based antimicrobial composition contained approximatelv 10% waterbv weight.

EXAMPLE 9B

Aquaphor@ Plus Water

A hydrated silver-based antimicrobial compositionwas made where the composition base was Aquaphor" The composition was madebv mixing 9.5 g of the silver-basedantimicrobial composition of Example 7 with 0.5 ml of water. This silver-based antimicrobial composition contained approximatelv 500 water.

EXAMPLE 9C

White Petrolatum PlusWater

A hydrated silver-based antimicrobial compositionwas madewhere thecomposition baseas white petrolatum. Tie compositionwas made by mixing 9 5 g of the silver-based antimicrobialcoin position of Example X with 0 5ml ofwater This silver-based antimicrobiaicomposition containedapproximately i"o water.

EXAMPLE 9D

Velvachol Cream

A silver-based antimicrobial composition containing0.47 g of the silver thiosulfate ion complexes of Example I were stirred into 20 g of Velvacholw (Owen Laboratories).

Velvachol@ is a neutral.hvdrophilic cream which contains some water (amount unknown).

The amount of silver in this silver-based antimicrobial composition was equivalent to 1.0% silver nitrate.

The stability of the silver-based compositions of Examples 6. 7, 8,and 9A-D was evaluated over time. Thestabilitv of the compositions was determinedbv measuring the change of color. ifanv. when the compositions were stored in transparent containers in ambient light. Change of color indicates decomposition of the silver thiosulfate ion complexes Table I below Indicates the Initial color of each composition and the change in color ondavs 7 and 14 and after I month.

As depictedbv the results of this study, the silver-based compositions described in

Examples 6. 7 and8 demonstrated no change in color. In contrast. thehvdrated silver-based compositions. Examples 9A-D, demonstrated malor changes In color. some after only 7davs (Examples 9B andOD), all of these compositions.i.e., Examples9A-D. changed from their initial color to a brown or black color. Thus, the results of thisstudv indicate that the anhydrous compositions of this invention were stable.while the analogoushydrated samples were not

TABLE I

Stability Of Silver-Based Compositions

EMI38.1

<tb> <SEP> Appearance <SEP> of <SEP> Ointment

<tb> <SEP> Sample

<tb> <SEP> Day <SEP> I <SEP> ~ <SEP> Day <SEP> 7 <SEP> Day <SEP> 14 <SEP> Month <SEP> I <SEP> Month <SEP> 3 <SEP> Month <SEP> 7

<tb> Example <SEP> 6: <SEP> PEG <SEP> Gravish <SEP> No <SEP> No <SEP> No <SEP> No <SEP> No

<tb> Composition <SEP> White <SEP> Change <SEP> Change <SEP> Change <SEP> Change <SEP> Change

<tb> Example <SEP> 7 <SEP> Aquaphor@ <SEP> <SEP> Slight <SEP> No <SEP> No <SEP> No <SEP> No <SEP> No

<tb> Composition <SEP> Yellow <SEP> Change <SEP> Change <SEP> Change <SEP> Change <SEP> Change

<tb> Example <SEP> 8: <SEP> White <SEP> Slight <SEP> No <SEP> No <SEP> No <SEP> No <SEP> No

<tb> Petrolatum <SEP> Composition <SEP> Yellow <SEP> Change <SEP> Change <SEP> Change <SEP> Change <SEP> Change <SEP> Change <SEP>

<tb> Example <SEP> 9A: <SEP> Hydrated <SEP> Grayish <SEP> No <SEP> Slight <SEP> Tan <SEP> Brown <SEP> Brown <SEP> Black

<tb> PEG <SEP> Composition <SEP> White <SEP> Change <SEP>

<tb> Example <SEP> 9B: <SEP> Hydrated <SEP> Slieht <SEP> Slight <SEP> Brown <SEP> D;irk <SEP> Black <SEP> Black

<tb>Aquaphor@ <SEP> <SEP> Composition <SEP> Yellow <SEP> Tan <SEP> Brown

<tb> Example <SEP> 9C <SEP> H@drated <SEP> <SEP> Slight <SEP> No <SEP> Tan <SEP> Black <SEP> Black <SEP> Black

<tb> White <SEP> Petrolatum <SEP> Yellow <SEP> Change

<tb> Composition

<tb> Example <SEP> 9D: <SEP> Velvachol@ <SEP> <SEP> White <SEP> Tan <SEP> Brown <SEP> Black <SEP> Black <SEP> Black

<tb>Cream <SEP>

<tb> 111.ANTIMICROBIAL ACTIVITY OF COMPOSITIONSCONTAINING

SILVER THIOSULFATE ION COMPLEXES

EXAMPLE 10

Antimicrobial Activity Of Silver Thiosulfate ion Complexes

The in vitro antimicrobial activity was evaluated by finding the minimum inhibitory concentration for the powder of silver thiosulfate ioncomplexes from Example; This powder was tested in serial two-fold dilutions ranging from l ')5 to250 g/ml. Broth microdilution was performed in serial dilution of the silverthiosulflite powder in tryptic sov broth (Difco) Each dilution was inoculated with 0 005 ml of a 24-hour growthol' a microbe (10 to10 CFU/ml). After the dilutions were incubated at 37 C overnight, the lowest dilution of the silver thiosulfate ion complexes that waswithout evidence of growth(i.e. was notcloudv) was the minimum inhibitorv concentration (MIC) reported in terms of g/ml

The results shown in Table2 demonstrate that the silver thiosulfate ion complexes powder has antimicrobialactivitv against both gram (+) and gram (-) microbes (Difco).

*TABLE 2

EMI39.1

<tb> <SEP> Isolate <SEP> ATCC <SEP> Accession <SEP> No. <SEP> Silver <SEP> Thiosulfate <SEP> Ion <SEP> Complexes <SEP> (g/ml)

<tb> <SEP> S <SEP> aureus <SEP> 25923 <SEP> < 1 <SEP> 95

<tb> S. <SEP> epidermidis <SEP> 12228 <SEP> 1 <SEP> 95

<tb> <SEP> E <SEP> coh <SEP> 25922 <SEP> < 1.95

<tb> P <SEP> aerugmosa <SEP> 27853 <SEP> 1 <SEP> 95

<tb>

EXAMPLE 11

AntimicrobialActivitv Of Silver-Based Compositions

The antimicrobial activitv of the silver-based compositions of Examples6. 7. and 8 were evaluated using a zone of inhibition (ZOI) protocol In this ZOI protocol. @ cmdiameter discs (Whatman Filter Paper, Quantitativel) were coated with a thin layer of the compositions from Examples6. 7. and 8 These coated discs were placed onMueller Hinton

Medium (MHM, Difco) with lawns of S.@ureus (ATCC25923, 24 hours growth from MHM plate)After incubation at 36 C for 18 hours. the size of the zone of growth inhibition was measured (in mm)from the edge of the disc to the point ofmicrobial growth Table 3 shows the ZOI resultstbr each composition onDav l and at one month.

TABLE 3

Antimicrobial Activity Of Silver-Based Compositions

EMI39.2

<tb> Zone <SEP> of <SEP> Inhibition <SEP> (mm) <SEP> (S. <SEP> aureus)

<tb> <SEP> Sample

<tb> <SEP> Day <SEP> 1 <SEP> 1 <SEP> Month

<tb> <SEP> Example <SEP> 6@ <SEP> PEG <SEP> Composition <SEP> 13.5 <SEP> mm <SEP> 14.0 <SEP> mm

<tb> Example <SEP> 7 <SEP> Aquaphor@

<tb> 10.0 <SEP> mm <SEP> 13.0 <SEP> mm

<tb> <SEP> Composition

<tb> <SEP> Example <SEP> 8@ <SEP> White <SEP> Petrolatum

<tb> <SEP> 10.0 <SEP> mm <SEP> 10.5 <SEP> mm

<tb> Composition

<tb>

As can be seenbv the results of this study, the sllver-based coin positions of this

Invention (Exampleso. 7 and 8) demonstrated good antimicrobial activity that was stable for the duration of thestudv period That is to sav. the siz

IV. USE OF SILVER THIOSULFATE ION COMPLEXES IN MEDICAL

DEVICES

EXAMPLE 12

Foam DressingsContaining Silver Thiosulfate Ion Complexes

As previously indicated. the silver thiosulfate ion complexes of the present invention can be used in coniunction with medical devices. This example Illustrates the use of silver thiosulfate ion complexes to prepare a medical device made up of a foam polymer matrix. In this example, the complexes were Incorporated into the matrix during the manufacturing of the polymer matrix.

A foam dressing was produced bv first dissolving0 g of silver thiosulfate ioncomplexes powder in 150 mlof aU 5%Pluronic L-62 (BASF) aqueous solution This solution was the mixed with140 g of a polyurethane prepolvmer (Hypol 2002, Hampshire) in a l-liter disposable plastic beaker The resulting mixture Instantlv began to react to form a

lbam. After 10 minutes the foamwas removed from Its container and sliced to produce individual foam dressings (approximately·75 cm in diameter Tile slices of foam dressings were dried at50 C in a dark convection oven.

These foam dressings were light stable and antimicrobiallv active In this example and

Examples 13-18 that follow, the terms "light stable." "photostable." and the like Inean that the samples did not discolor after 72hours of exposure to ambient roomlight In this exampleind Exaniples 13-I 8 that follow. the term@antimicrobially active' means that a small piece (nominally I cm x I cin or lcm strands in the case of alginate fibers) produced zonesot inhibition when placed on both a lawn of S. aureus (ATCC 25923) and a lawn of E. coli

ATCC 25922).The lawns were producedbv plating 24-hour growth microbes on MHMrelates: after incubation for24 hours. each sample was examined to determine whether a zone of inhibition was present

This foamdressing can be used for a large variety of medical applications.including as anantimicrnbial absorptivelbam dressing.

EXAMPLE 13

Foam Dressing Containing Silver Thiosulfate Ion Complexes

This example further illustratesthe use of silver thiosulfate ion complexes to prepare a medical device made up of a foam polymer matrix. In contrast to the previous example. the silver thiosulfate ion complexes were incorporated into polymer matrix following the matrix' manufacture.

In this example, a foam dressing (Hvdrasorb" Sponge Foam Dressing (10 cm x 10 cm); Avitar) was submerged in an aqueous solution containing silver thiosulfate ion complexes powder from Example 3 (0. 1 g per liter). The foam dressing samples were removed and dried at 50 C in a convection oven.These silver thiosulfate ion complexecontaining foam dressings were light stable and antimicrobiallv active. As indicated in the previous example. these foam dressings can be used for a large varietyof medical applications. including as an antimicrobial absorptive foam dressings.

EXAMPLE 14

Hydrocolloid Dressing Containing Silver Thiosulfate Ion Complexes

This example illustrates the use of thesilver thiosulfate ion complexes to prepare amedical device which is made up of a hydrocolloid absorbent polymer matrix. In this example.tlie complexeswere Incorporated into thematrix during themanufacturin' oftl1e polvmer matrix

A hvdrocolloid dressing containingsliver thiosulfate ion complexes was produced bvtirst thoroughly mixing 0.157 g of silver thiosulfate ion complexes powder (mesh 100) from

Example I with 10.0 g of sodium carboxvmethvl cellulose(Aldrich). Thereafter. 4 g of this treated carboxvmethvl cellulose was mixed thoroughly with 4 g of apolvurethane prepolvmer (Aquapol 035-0031, Cook Composites andPolymers). Thismixture was then pressed between a polyurethane film and a silicone-treated hvdrocolloidmatrix and was allowed to cure for24 hours.

The resulting silver thiosulfate ioncomplexes-containing hvdrocolloid dressing was photostable and antimicrobiallv active Thistvpe of dressing isuseful onexudating, malodorous wounds.

EXAMPLE 15

Hydrocolloid Dressing Containing Silver Thiosulfate Ion Complexes

This example further illustrates the use of silver thiosulfate ion complexes of this

Invention to prepare a medical device which is made up of an hvdrocolloid absorbent polymer matrix However. in this example the silver thiosulfate ion complexes were incorporated into the polymer matrix by a different procedure than that presented in the preceding example.

The hydrocolloid dressing was produced by first dissolving 0 157, of a silver thiosulfate ion complexes powder (mesh > 100) from Example I in 100 ml of water. To this solution was added 100 g of sodium carboxvmethvl cellulose (Aldrich. Milwaukee, Wl) which absorbed the solution The treated sodium carboxymethvl cellulose was allowed to dry at room temperature Thereafter, 4'2 of the dried treated carboxymethyl cellulose was mixed thoroughly with 4 g ot' a polyurethane prepolvmer (Aquapol 035-0031, Cook Composites and

Polymers). This mixture was then pressed between apolvurethane film and a silicone treated liner and was allowed to curefor 24 hours.

As with the silver thiosulfate ioncomplexes-containing hvdrocolloid dressing produced

In the preceding example. thehvdrocolioid dressing Is photostable and antimicrobially active and Is useful on exudating, malodorous wounds.

EXAMPLE16

AdhesiveFiims Containing Silver Thiosulfatelon Complexes

This example Illustrates the use of silver thiosulfate ioncomplexes to produce adhesive

films.Specifically. a pressure sensitive adhesive (PSA) containing silver thiosulfate ion

complexes was produced in this example.Adhesive films are. among other things,especially

useful in covering painful abrasive-tvpe skin wounds and partial skin graft sites.

The silver thiosulfate ioncomplexes-containing PSA was madebv mixing 025 g of

the silver thiosulfate ion complexes powder from Example I In An adhesive solution

consisting of 45g of a proprietary medical grade acrylic based latex (58% solids) (Avery

Dennison. Inc.) andS g polvethvlene glycol (M.W 600)(Aldrich) was first prepared Then.

0.25 g of the silver thiosulfate ion complexes powder from Example I was mixed withthe

adhesive solution.forming an adhesive mixture. This adhesivemixture. alien coated and

dried, produces a tackv. adhesive film

The adhesive film is photostable and antimicrobially active This adhesive film can be laminated to dressing backing materials to produce dressings which are antimicrobiallv active.

Dressings with the silver thiosulfate ioncomplexes-containing PSA are especially useful in coveringpainful abrasive-tvpe skin wounds and partial skin graft sites.

EXAMPLE 17

Alginate Materials Containing Silver Thiosulfate Ion Complexes

This example illustrates the use of silver thiosulfate ion complexes to produce a medical device which is made up of non-adherent alginate material. Specifically, the method of this example involves the use of a calcium chloride bathwhich results In crosslinkedalginate fibers that incorporate the silver thiosulfate ion complexes

I'irst. water-swellable alginate fibers were produccdcontaining silver thiosulfate ion complexes. The alginate fibers were made by using a svringe to inject a 5% sodiumalginate solution (Pronova LVhl Sodiumalginate. Protan) into a bath consisting of a 10% calcium chloride solutionAldrich. deionized water as diluent) containing0 1 g/liter silver thiosulfate ion complexes powder from Example3 Thealuinate solutionimmediately formedwater insolublealginate fibers upon contactwith the calcium chlorlde/sllver thiosulfate ion complexes bath The fibers were pulled from the bath and allowed to dry (50 C).

The resulting fibers are photostable and antimicrobiallv activeThese fibers can be used tomake antimicrobial alienate dressings and tamponades. Alginate materials containing silvertliiosulfate ioncomplexes areespecially useful Incowering painful abrasive-tvpe skinwounds and wound ulcers as well as torfilling in deep wounds and cavities.

EXAMPLE 18

Alginate Materials Containing Silver Thiosulfate Ion Complexes

To further illustrate the use of the silver thiosulfate ion complexes of this invention to produce a medical device which is made up on non-adherent alienate material. this exampleutilizes a method that does not include a calcium chloride bath

First. an aqueous solution containing 0. 1 g/liter of a silver thiosulfate ion complexes from Example 3 was prepared. The resulting aqueous solution was then applied to a 9.5 cm x() 5 cm alginate dressing (Steriseal SorbsanSurgical Dressing. Steriseal)bv spraying the solution onto the dressing. Alternatively, the silver thiosulfate ion complexes solution can be appliedbv dipping thealginate dressing into the solution. Thealginate fibers of the dressing absorbed the applied solution: thereafter. the treatedalginate dressingwas allowed to dry (room temperature).

The alginatedressing was light stable and was antimicrobialiv active, and, as noted in the preceding example. It is especially useful for malodorous wounds as well as for covering painful abrasive-tvpe skin wounds and wound ulcersUSE OF SILVER THIOSULFATE ION COMPLEXES IN COMBINATION

WITH OTHER MEDICINAL AGENTS

EXAMPLE19

Pharmaceutical Composition Combining Mupirocin

With SilverThiosulfate Ion Complexes

To illustrate an antimicrobial pharmaceutical composition consisting of a combination of the silver thiosulfate ion complexes of the present invention with one or moreagents 0.02 of the silver thiosulfate ion complexes from Example2 were blended into 2.0g of a

mupirocin

ointment (Bactroban"

[n

mupirocin acid in a PEG bases, SmithKline Beecham)

The mupirocin ointment is a topical antimicrobial

with

excellent gram (+) antimicrobial properties The silver thiosulfate ion complexes

were

blended into the

mupirocin

ointment bv first melting the mupirocin

ointment

and then stirring the silver thiosulfate ion complexes Into the melted ointment

Tlie

ointment was stirred continually

until

it cooled and resolidified

EXAMPLE

20

Pharmaceutical Composition Combining Mafenide

With Silver

Tliiosulfate

Ion ('oinplexes

To further illustrate an antimicrobial

0 25 g of mafenide(Sigma) (p-aminomethylbenzesulfonamide) and 0.25 g of the silver thiosulfate ion complexes of Example 3 were blended into24.50 g of a PEG composition ("PEG Composition"); the PEG Compositionwas producedbv melting together a blendot 40% PEG (M.W.3450) and 60% PEG (M.W. 600). The pharmaceutical composition was producedbv firstmelting the PEG Composition and then stirring In the silver thiosulfate ion complexes and mafenide. The resulting pharmaceutical composition was stirred continually until cooled and resolidified. The resulting pharmaceutical composition has use as a broad spectrum topical antimicrobial.

EXAMPLE 21

Pharmaceutical Composition Combining Metronidazole

With Silver Thiosulfate Ion Complexes

To further illustrate an antimicrobial pharmaceutical composition consisting of a combination of the silver thiosulfate ion complexes of the present invention with one or more agents. 0.25 g of metronidazole(Sigma? and 0.25g of the silver thiosulfate ion complexes of

Example 3 were blended Into24.50 g of a PEG composition ("PEG Composition"); the PEG

Composition was producedbv melting together a blend of 40% PEG (M.W.34503 and 60%

PEG (M.W 600). The pharmaceutical composition was producedbv firstmelting the PEG

Composition and then stirring Intlie silver thiosulfate ion complexes and metronidazole. The resulting pharmaceutical composition was stirred continually until it cooled and resolidified.

This pharmaceutical composition has use as a broad spectrum topical antimicrobial and is especially useful in the treatment of malodorous wounds

EXARIPLE 22

Pharmaceutical Composition Combining Chlorhexidine

With Silver Thiosulfate Ion Complexes

To further illustrate anantimicrobiaf pharmaceutical composition consisting of a combination of the silver thiosulfate ion complexes of the present Invention with one or more agents. 0.25 g of chlorhexidine diacetatehvdrate (Aldrich) and 0.25g of the silver thiosulfate ion complexes of Example3 were blended into 24.5 gof Aquaphor@ (a cholesterolized absorbent EuceriteK ointment base producedbv Belersdorf Inc.). The pharmaceutical composition was produced by firstmeltinfr theAquaphor@ ointment and then stirring in the silver thiosulfate ion complexes and chlorhexidine. The resulting pharmaceutical composition was stirred continually until it cooled and resolidified. This pharmaceutical composition has use as a broad spectrum topical antimicrobial.

EXAMPLE 23

Pharmaceutical Composition Combining Triclosan

With SilverThiosult'ate Ion Complexes

To further illustrate an antimicrobial pharmaceutical composition consisting of a combination of the silver thiosulfate ion complexes of the present invention with one or more medicinal agents. 0.50g of triclosan (Irgasan DP 300.Ciba-Geigy, Greensboro, NC) and 0.50of the silver thiosulfate ion complex of Example ;were blended into 24.00g of Aquaphor@ (a cholesterolized absorbentEucerite" ointment base produced bv Belersdorf Inc.). The pharmaceutical compositionwas produced bv thirst melting theAquaphor@ ointment and thenstirring in the silver thiosulfate ion complexes and triclosan The resulting pharmaceutical composition was stirred continually until It cooled and resolidified This pharmaceutical composition has use as a broad spectrum topical antimicrobial.

EXAMPLE 24

Pharmaceutical CompositionCombining Hydrocortisone

With SilverThiosultate Ion Complexes

To further Illustrate an antimicrobial pharmaceutical composition consisting of a combination of the silver thiosulfateloll complexes of the presentinvention with one or more agents. 0.50 g of Hvdrocortisone21-Acetate (Sigma) and 050 g ol' the silver thiosulfate ioncomplexes of Example 3 were blended into24.00 g ofAquaphor@ (a cholesterollzed absorbentEucerite@ ointment base produced bv Belersdorf Inc.) The pharmaceutical composition was producedbv first melting theAquaphor@ ointment and thenstirring In the silver thiosulfate ion complexes and hydrocortisone. Theresulting pharmaceutical composition was stirred continually until it cooled and resolidified. This pharmaceutical composition has use topicallv as ananti-inflammatory and an anti-itch treatment which also has antimicrobial properties to prevent a secondary infection when applied topically to blistered wounds causedbv dermatitis.

insect bites, poisonivy, etc.

EXAMPLE 25

Pharmaceutical Composition Combining Lidocaine With

Silver thiosulfate Ion Complexes

To further illustrate an antimicrobial pharmaceutical composition consisting of a combination of the silver thiosulfate ion complexes of the present invention with one or more agents. 0.50 g of lidocaine (Sigma) and 0.50 of the silver thiosulfate ion complexes of

Example3 were blended into24.00 g of PEG composition ("PEG Composition"), the PEG

Composition was produced by melting together a blend of 40% PEG (M.W. 3450) and 60%

PEG(Ni W.) The pharmaceutical composition was produced by first melting the PEG

Composition and then stirring in the silver thiosulfate ion complexes and lidocaine. The resulting pharmaceutical composition was stirred continually until it cooled and resolidified.

Thispharmaceutical composition has use as a topical anesthetic which also has antimicrobial properties to prevent a secondary infectionwhen applied to exposed tissues or wounds.

EXAMPLE 26

PharmaceuticalComposition CombiningPramoxine With

Silver Thiosulfate IonComplexes

To further illustrate an antimicrobial pharmaceutical composition consisting of a combination of the silver thiosulfate ion complexes of the present inventionwith one ormore agents IO() (of pramoxinehvdrocl1loride (Sigma) and ()"0 gof the silver thiosulfate ion complexes of Example3 severe blended into23.50 g of PEG composition(l'PEG

Composition"); the PEG Compositionwas producedbv melting together a blend of40 0 PEG(M.W. 3450) and 60% PEG (M.W600). The pharmaceutical compositionwas producedbv first meltiny the PEG Composition and then stirring in the silvertliiosulfate ion complexes and pramoxineTlie resulting pharmaceutical compositionwas stirred continually until It cooled and resolidified. This pharmaceutical composition has use as a topical anestheticwhich also has antimicrobial properties to prevent a secondary infection when applied to exposed tissues or wounds

From the above, it should be evident that the present invention provides for silverbased antimicrobial compositions and processes for making such compositions that are suitable for use in the treatment and prevention of infections It should be understood thatthe present Invention is not limited to the specific compositions shown nor to the uses of the compositions described. In light of theforegoing disclosure, it will be apparent to those skilled in the art that substitutions. alterations. and modifications are possible in the practice of this Invention without departing from the spirit or scope thereof.